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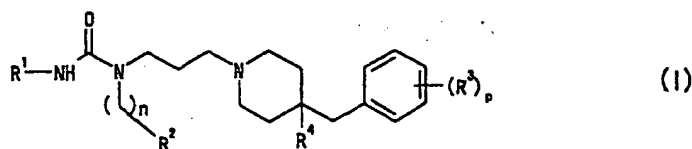
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(54) **UREA COMPOUNDS, PROCESS FOR PRODUCING THE SAME AND USE THEREOF**

(57) A compound of the formula:



[wherein

R¹ is a hydrocarbon group which may be substituted;
R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;
R³ is halogen atoms, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted,
an acyl group derived from sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which
may be substituted, an amino group which may be substituted, a nitro group or a cyano group;
R⁴ is hydrogen atoms or a hydroxy group;
n is 0 or 1; and
p is 0 or 1 to 4];

or a salt thereof, has potent CCR5 antagonistic activity and can be advantageously used as a medicament for inhibition
of HIV infection to human peripheral blood mononuclear cells, especially for the treatment or prevention of AIDS.

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R⁴ is a hydrogen atom or a hydroxy group;

n is an integer of 0 or 1;

p is an integer of 0 or 1 to 4];

or a salt thereof,

(2) the compound as shown in the above (1), wherein R³ is a halogen atom, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group,

(3) the compound as shown in the above (1), wherein R¹ is an alicyclic hydrocarbon group which may be substituted or an aryl group which may be substituted,

(4) the compound as shown in the above (1), wherein R¹ is a hydrocarbon group which may be substituted by 1 to 4 substituent(s) selected from 1) a hydrocarbon group which may be substituted, 2) an heterocyclic group which may be substituted, 3) a C₁₋₄ alkoxy group which may be substituted, 4) a C₁₋₄ alkylthio group which may be substituted, 5) a C₂₋₆ alkoxycarbonyl group which may be substituted, 6) a C₁₋₆ alkanoyl group which may be substituted, 7) an amino group which may be substituted, 8) a cyclic amino group, 9) a halogen atom, 10) a nitro group, 11) a cyano group, 12) a carbamoyl group which may be substituted, 13) a sulfamoyl group which may be substituted and 14) an acyl group derived from a sulfonic acid,

(5) the compound as shown in the above (1), wherein R¹ is a hydrocarbon group which may be substituted by 1 to 4 substituent(s) selected from 1) a hydrocarbon group which may be substituted, 2) a heterocyclic group which may be substituted, 3) a C₁₋₄ alkoxy group which may be substituted, 4) a C₁₋₄ alkylthio group which may be substituted, 5) a C₂₋₆ alkoxycarbonyl group which may be substituted, 6) an amino group which may be substituted, 7) a halogen atom, 8) a nitro group and 9) a cyano group,

(6) the compound as shown in the above (1), wherein R¹ is a hydrocarbon group which may be substituted by 1 to 4 substituent(s) selected from 1) a hydrocarbon group which may be substituted, 2) a heterocyclic group which may be substituted, 3) a C₁₋₄ alkylthio group which may be substituted, 4) a C₂₋₆ alkoxycarbonyl group which may be substituted, 5) an amino group which may be substituted, 6) a halogen atom and 7) a nitro group,

(7) the compound as shown in the above (1), wherein R² is an cyclic hydrocarbon group which may be substituted,

(8) the compound as shown in the above (1), wherein R³ is a halogen, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted or an acyl group derived from a sulfonic acid,

(9) the compound as shown in the above (1), wherein R³ is a halogen,

(10) the compound as shown in the above (1), wherein R⁴ is a hydrogen atom,

(11) the compound as shown in the above (1), wherein n is 0,

(12) the compound as shown in the above (1), wherein R¹ is a hydrocarbon group selected from Group 3 which may be substituted by member(s) selected from Group 1; R² is a cyclic hydrocarbon group selected from Group 10 which may be substituted by member(s) selected from Group 2, or a heterocyclic group selected from Group 4 which may be substituted by member(s) selected from Group 2; R³ is a halogen atom, a carbamoyl group, a N-mono-substituted carbamoyl group which is substituted by a member selected from Group 11, a N,N-di-substituted carbamoyl group which is substituted by a member selected from Group 11 and a member selected from Group 14, a cyclic aminocarbonyl group selected from Group 17, a sulfamoyl group, N-mono-substituted sulfamoyl group which is substituted by a member selected from Group 11, a N,N-di-substituted sulfamoyl group which is substituted by a member selected from Group 11 and a member selected from Group 14, a cyclic aminosulfonyl group selected from Group 20, an acyl group derived from a sulfonic acid selected from Group 15, a C₁₋₄ alkyl group which may be substituted by member(s) selected from Group 2, a C₁₋₄ alkoxy group which may be substituted by member(s) selected from Group 2, an amino group which may be substituted by member(s) selected from Group 8, a cyclic amino group selected from Group 9, a nitro group or a cyano group.

[In the above,

Group 1 includes

1) a hydrocarbon group which selected from Group 3 which may be substituted by member(s) selected from Group 2, 2) a heterocyclic group which selected from Group 4 which may be substituted by member(s) selected from Group 2, 3) a C₁₋₄ alkoxy group which may be substituted by member(s) selected from Group 2, 4) a C₁₋₄ alkylthio group which may be substituted by member(s) selected from Group 2, 5) a C₂₋₆ alkoxycarbonyl group which may be substituted by member(s) selected from Group 2, 6) a C₁₋₆ alkanoyl group, 7) an amino group which may be substituted by member(s) selected from Group 8, 8) a cyclic amino group selected from Group 9, 9) a halogen atom, 10) a nitro group, 11) a cyano group, 12) a carbamoyl group, 13) a mono-substituted carbamoyl group which is substituted by a member selected from Group 11, 14) di-substituted carbamoyl group which is substituted by a member selected from Group 11 and a member selected Group 14, 15) a cyclic amino carbamoyl group selected from Group 17, 16) a sulfamoyl group, 17) a N-mono substituted sulfamoyl group which is substituted by a member selected from Group 11, 18) a N,N-di-substituted sulfamoyl group which is substituted by a member selected from

Group 11 and a member selected Group 14, 19) an acyl group derived from a sulfonic acid selected from Group 19, Group 2 includes

1) a C₁₋₆ alkoxy group, 2) a halogen atom, 3) a C₁₋₆ alkyl group, 4) a C₁₋₄ alkynyl group, 5) an amino group, 6) a hydroxy group, 7) a cyano group and 8) an amidino group,

Group 3 includes

1) a C₁₋₆ alkyl group, 2) a C₃₋₆ cycloalkyl group and 3) a C₆₋₁₄ aryl group,

Group 4 includes

1) an aromatic monocyclic heterocyclic group selected from Group 5, 2) an aromatic condensed heterocyclic group selected from Group 6 and 3) a saturated or unsaturated non-aromatic heterocyclic group selected from Group 7,

Group 5 includes

furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl,

Group 6 includes

benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzindazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, benzopyranyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidiny, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indoliziny, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[4,3-b]pyridazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl,

Group 7 includes

oxylanyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl,

Group 8 includes

1) a C₁₋₆ alkyl, 2) a C₁₋₆ alkanoyl, 3) a C₇₋₁₃ arylcarbonyl, 4) an optionally halogenated C₂₋₆ alkoxy carbonyl, 5) a C₁₋₆ alkylimidoyl, 6) a formylimidoyl and 7) an amidino,

Group 9 includes

1) 1-azetidiny, 2) 1-pyrrolidinyl, 3) 1-piperidinyl, 4) 4-morpholinyl, 5) 1-piperazinyl and 6) 1-piperazinyl which may have a C₁₋₆ alkyl, a C₇₋₁₀ aralkyl and a C₆₋₁₀ aryl at 4-position,

Group 10 includes

C₃₋₉ cycloalkyl, 1-indanyl, 2-indanyl, C₃₋₆ cycloalkenyl, C₄₋₆ cycloalkanedienyl and C₆₋₁₄ aryl,

Group 11 includes

1) a C₁₋₆ alkyl group which may be substituted by member(s) selected from Group 12, 2) a C₃₋₆ cycloalkyl group which may be substituted by member(s) selected from Group 12, 3) a C₆₋₁₀ aryl group which may be substituted by member(s) selected from Group 12, 4) a C₇₋₁₀ aralkyl group which may be substituted by member(s) selected from Group 12, 5) a C₁₋₆ alkoxy group which may be substituted by member(s) selected from Group 12 and 6) a heterocyclic group selected from Group 13 which may be substituted by member(s) selected from Group 12,

Group 12 includes

1) a hydroxy group, 2) an amino group, 3) an amino group which is mono or di-substituted by member(s) selected from Group 16, 4) a halogen atom, 5) a nitro group, 6) a cyano group, 7) a C₁₋₆ alkyl group which may be substituted by halogen atom(s) and 8) a C₁₋₆ alkoxy group which may be substituted by halogen atom(s),

Group 13 includes

1) an aromatic heterocyclic group selected from Group 5 and Group 6 and 2) a saturated or unsaturated non-aromatic heterocyclic group selected from Group 7, each of which contains at least one heteroatom(s) selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom,

Group 14 includes

a C₁₋₆ alkyl group, a C₃₋₆ cycloalkyl group and a C₇₋₁₀ aralkyl group,

Group 15 includes

1) a C₁₋₁₀ alkylsulfonyl which may be substituted by member(s) selected from Group 12, 2) a C₂₋₆ alkenylsulfonyl which may be substituted by member(s) selected from Group 12, 3) a C₂₋₆ alkynylsulfonyl which may be substituted by member(s) selected from Group 12, 4) a C₃₋₉ cycloalkylsulfonyl which may be substituted by member(s) selected from Group 12, 5) a C₃₋₉ cycloalkenylsulfonyl which may be substituted by member(s) selected from Group 12, 6) a C₆₋₁₄ arylsulfonyl which may be substituted by member(s) selected from Group 12 and 7) a C₇₋₁₀ aralkylsulfonyl which may be substituted by member(s) selected from Group 12,

Group 16 includes

a C₁₋₆ alkyl group, a C₁₋₆ alkanoyl, a C₇₋₁₃ arylcarbonyl and a C₁₋₆ alkylsulfonyl,

Group 17 includes

1-azetidinylicarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, 4-morpholinylcarbonyl and 1-piperazinylcarbonyl which may be substituted by member(s) selected from Group 18,

Group 18 includes

a C₁₋₆ alkyl group, a C₇₋₁₀ aralkyl group and a C₆₋₁₀ aryl group,

Group 19 includes

a C₁₋₁₀ alkylsulfonyl which may be substituted by member(s) selected from Group 12, a C₂₋₆ alkenylsulfonyl which may be substituted by member(s) selected from Group 12, a C₂₋₆ alkynylsulfonyl which may be substituted by member(s) selected from Group 12, a C₃₋₉ cycloalkylsulfonyl which may be substituted by member(s) selected from Group 12, a C₃₋₉ cycloalkenylsulfonyl which may be substituted by member(s) selected from Group 12, a C₆₋₁₄ arylsulfonyl which may be substituted by member(s) selected from Group 12, and a C₇₋₁₀ aralkylsulfonyl which may be substituted by member(s) selected from Group 12, and

Group 20 includes

1-azetidinylsulfonyl, 1-pyrrolidinylsulfonyl, 1-piperidinylsulfonyl, 4-morpholinylsulfonyl and 1-piperazinylsulfonyl which may be substituted by member(s) selected from Group 18],

(13) the compound as shown in the above (1), wherein R¹ is a C₃₋₈ cycloalkyl group which may be substituted by member(s) selected from Group 1 or a C₆₋₁₄ aryl group which may be substituted by member(s) selected from Group 1, (14) the compound as shown in the above (12), wherein R¹ is 1) a C₆₋₁₄ aryl group which may be substituted by a halogen atom, a C₁₋₆ alkyl which may be substituted by halogen(s), a C₁₋₄ alkylthio, a nitro, a carbamoyl, a sulfamoyl or a C₁₋₆ alkylsulfonyl, 2) a C₁₋₆ alkyl group which may be substituted by (i) a C₂₋₆ alkoxy carbonyl group or (ii) a C₁₋₆ alkyl group which may be substituted by phenyl(s) which may be substituted by C₁₋₆ alkyl(s) or 3) a C₃₋₈ cycloalkyl group which may be substituted by (i) a halogen atom, (ii) a C₁₋₆ alkyl(s) which may be substituted by halogen(s) or (iii) a C₁₋₆ alkoxy group which may be substituted by halogen(s);

R² is a phenyl group which may be substituted by a halogen atom, a C₁₋₆ alkyl, a C₁₋₄ alkoxy or a cyano, a C₃₋₈ cycloalkyl group or a pyridyl group;

R³ is (i) a halogen atom, (ii) a carbamoyl group, (iii) a sulfamoyl group which may have one or two C₁₋₆ alkyl(s) or C₃₋₆ cycloalkyl(s) at N-atoms, (iv) a cyclic aminosulfonyl group which is selected from Group 20, (v) a C₁₋₆ alkylsulfonyl group or (vi) C₃₋₆ cycloalkylsulfonyl group;

R⁴ is a hydrogen atom;

n is 0 or 1 and

p is 0 or 1,

(15) the compound as shown in the above (12), wherein R¹ is 1) a phenyl which may be substituted by a halogen atom, a C₁₋₃ alkyl, trifluoromethyl, methoxy, trifluoromethoxy, methylthio or nitro, 2) a naphthyl, 3) a C₁₋₆ alkyl group which may be substituted by (i) a C₂₋₃ alkoxy carbonyl, (ii) phenyl or (iii) 3-isopropenylphenyl, or 4) cyclohexyl;

R² is a phenyl group which may be substituted by a halogen atom, methyl, methoxy or cyano, a cyclohexyl group or a 3-pyridyl group;

R³ is (i) a halogen atom, (ii) a carbamoyl group, (iii) a 4-morpholinylsulfonyl group or (iv) a methylsulfonyl group,

R⁴ is a hydrogen atom;

n is 0 or 1; and

p is 0 or 1,

(16) the compound as shown in the above (12), wherein R¹ is a phenyl group which may be substituted by a halogen atom or a C₁₋₃ alkyl; R² is a phenyl group which may be substituted by a halogen atom and methyl(s);

R³ is (i) a halogen atom, (ii) a carbamoyl group, (iii) a sulfamoyl group which may be substituted by one or two members selected from the group consisting of C₁₋₆ alkyl and C₃₋₆ cycloalkyl at N-atoms, a cyclic aminosulfonyl group selected from Group 20, a C₁₋₆ alkylsulfonyl group or a C₃₋₆ cycloalkyl sulfonyl group;

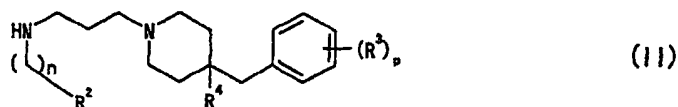
R⁴ is a hydrogen atom;

n is 0; and

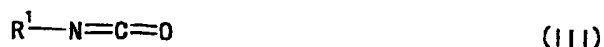
p is 0 or 1,

(17) the compound as shown in the above (1), which is N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(4-chlorophenyl)-N-phenylurea, N'-(4-chlorophenyl)-N-[3-[4-(4-fluorobenzyl)-1-piperidinyl]propyl]-N-phenylurea, N'-(4-chlorophenyl)-N-[3-[4-(4-morpholinylsulfonyl)benzyl]-1-piperidinyl]propyl]-N-phenylurea, N'-(4-chlorophenyl)-N-[3-[4-(4-methylsulfonyl)benzyl]-1-piperidinyl]propyl]-N-phenylurea,

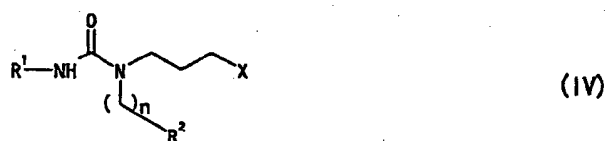
- 4-[[1-(3-[[[4-chloroanilino]carbonyl]anilino]propyl)-4-piperidiny]methyl]benzamide, or a salt thereof,
 (18) a prodrug of the compound of the formula (I) or a salt thereof,
 (19) a pharmaceutical composition containing a compound of the formula (I), a salt thereof or a prodrug thereof,
 (20) the pharmaceutical composition as shown in the above (19), which is a chemokine receptor antagonist,
 (21) the pharmaceutical composition as shown in the above (19), which is a CCR5 antagonist,
 (22) the composition as shown in the above (19), which is for the treatment or prevention of infectious disease of HIV,
 (23) the composition as shown in the above (19), which is for the treatment or prevention of AIDS,
 (24) the composition as shown in the above (19), which is for the prevention of the progression of AIDS,
 (25) the composition as shown in the above (22), further comprises a protease inhibitor and/or a reverse transcriptase inhibitor,
 (26) the composition as shown in the above (25), wherein the reverse transcriptase inhibitor is zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, nevirapine, delavirdine or efavirenz,
 (27) the composition as shown in the above (25), wherein the protease inhibitor is saquinavir, ritonavir, indinavir, amprenavir or nelfinavir,
 (28) use of a compound of the formula (I), a salt thereof or prodrug thereof for the manufacture of an antagonist of a chemokine receptor,
 (29) use of a compound of the formula (I), a salt thereof or prodrug thereof for the manufacture of a CCR5 antagonist,
 (30) use of a compound of the formula (I), a salt thereof or prodrug thereof, for the manufacture of a medicament for the treatment or prevention of infectious disease of HIV,
 (31) use of a compound of the formula (I), a salt thereof or a prodrug thereof for the manufacture of a medicament for the treatment or prevention of infectious disease of HIV which is used in combination with a protease inhibitor and/or a reverse transcriptase inhibitor,
 (32) a method for antagonizing CCR5 which comprises administering to a mammal in need thereof an effective amount of the compound of the formula (I), a salt thereof or a prodrug thereof,
 (33) a method for producing a compound of the formula (I) or a salt thereof, which comprises reacting a compound of the formula:



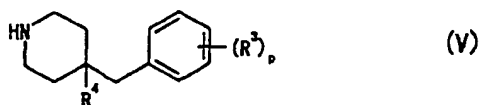
wherein each symbol has the meaning given above, or a salt thereof, with a compound of the formula:



wherein R¹ has the meaning given above, or a salt thereof,
 [0008] (34) a method for producing a compound of the formula (I) or salt thereof, which comprises reacting a compound of the formula:



wherein X is a leaving group, and other symbols have the meanings given above or a salt thereof, with a compound of the formula:



wherein each symbols has the same meaning given above, or a salt thereof in the presence of base.

[0009] Examples of the hydrocarbon group in the "a hydrocarbon group which may be substituted" represented by R¹ include, for example, an aliphatic hydrocarbon group, an alicyclic hydrocarbon group and an aryl group etc. Examples of the aliphatic hydrocarbon group include a C₁₋₆ alkyl group, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 1-methylpropyl, n-hexyl, isohexyl etc. Examples of the "alicyclic hydrocarbon group" include a C₃₋₈ cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc. Examples of the aryl group include a C₆₋₁₄ aryl group such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), etc, are preferred.

[0010] Examples of the substituent(s) in the "hydrocarbon group which may be substituted" represented by R¹ include a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₄ alkoxy group which may be substituted, a C₁₋₄ alkylthio group which may be substituted, a C₂₋₆ alkoxy carbonyl group which may be substituted, a C₁₋₆ alkanoyl group which may be substituted, an amino group which may be substituted, a nitro group, a cyano group, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, etc.

[0011] Examples of the hydrocarbon group(s) in the "hydrocarbon group which may be substituted" are those similar to the "hydrocarbon group" of the "hydrocarbon group which may be substituted", which is represented by R¹. Among these substituents, a C₁₋₆ alkyl group, a C₃₋₈ cycloalkyl group, a C₆₋₁₄ aryl group are preferred. These examples may include the substituents as mentioned above for R¹. Examples of the substituents in the "hydrocarbon group which may be substituted" include, for example, a lower alkoxy group (e.g., a C₁₋₆ alkoxy group such as methoxy, ethoxy, propoxy, etc.), a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a lower alkyl group (e.g., a C₁₋₆ alkyl group such as methyl, ethyl, propyl, etc.), a lower alkynyl group (e.g., a C₁₋₄ alkynyl group such as vinyl, 1-propenyl, 2-propenyl, isopropenyl, butenyl, isobutenyl, etc.), an amino group, a hydroxy group, a cyano group, an amidino group etc. The hydrocarbon in "hydrocarbon which may be substituted" may have 1 to 3 substituent(s) as described above at any possible position.

[0012] Examples of the heterocyclic group in the "heterocyclic group which may be substituted" (the substituent in the "hydrocarbon group which may be substituted by R¹") include, for example, an aromatic heterocyclic group, saturated or unsaturated non-aromatic heterocyclic group (alicyclic heterocyclic group) etc., which contains, besides carbon atoms, at least one heteroatom(s) (preferably 1 to 4 heteroatom(s), more preferably, 1 to 2 heteroatom(s)) consisting of 1 to 3 kind(s) of heteroatom(s) (preferably 1 to 2 kinds of heteroatom(s)) selected from an oxygen atom, a sulfur atom, a nitrogen atom, etc.

[0013] Examples of the "aromatic heterocyclic group" include an aromatic monocyclic heterocyclic group such as a 5 or 6-membered aromatic monocyclic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.); an aromatic fused heterocyclic group such as a 8 to 12-membered aromatic fused heterocyclic group (e.g., benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzindazolyl, benzoxazolyl, 1,2-benzisooxazolyl, benzothiazolyl, benzopyranyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indoliziny, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, etc.); etc., preferably, a heterocyclic group consisting of the above-mentioned 5- or 6-membered aromatic monocyclic heterocyclic group fused with a benzene ring or heterocyclic group consisting of the above-mentioned 5- or 6-membered aromatic monocyclic heterocyclic group fused with the same or different above-mentioned 5- or 6-membered aromatic monocyclic heterocyclic group, etc.

[0014] Examples of the "non-aromatic heterocyclic group" include a 3 to 8-membered (preferably 5 or 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocyclic group (aliphatic heterocyclic group) such as oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, etc.

[0015] Examples of the "substituent(s)" of the "heterocyclic group which may be substituted" (substituent(s) of the hydrocarbon group which may be substituted, which is represented by R¹) are those similar to the "substituent(s)" of the "hydrocarbon group which may be substituted" that is(are) the "substituent(s)" of the hydrocarbon group which may

be substituted, which is represented by R¹.

[0016] Examples of "C₁₋₄ alkoxy group" in the "C₁₋₄ alkoxy group which may be substituted" include, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, etc. Example of "C₁₋₄ alkylthio group" in the "C₁₋₄ alkylthio group which may be substituted" include, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, tert-butylthio, etc. Example of the "C₂₋₆ alkoxy carbonyl group" in "C₂₋₆ alkoxy carbonyl group which may be substituted" include, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, n-pentyloxycarbonyl, etc.

[0017] Examples of the "C₁₋₆ alkanoyl group" in the "C₁₋₆ alkanoyl group which may be substituted" include, for example, formyl, acetyl, propionyl, pivaloyl etc. Examples of the substituent in the "C₁₋₄ alkoxy group which may be substituted", "C₁₋₄ alkylthio group which may be substituted", and "C₁₋₆ alkoxy carbonyl group which may be substituted", "C₁₋₆ alkanoyl group which may be substituted" are those similar to the substituent(s) of the "hydrocarbon group which may be substituted", which are the substituent(s) of the "hydrocarbon group which may be substituted" represented by R¹.

[0018] Examples of the substituent(s) of the "amino group which may be substituted" include, for example, a lower alkyl group (e.g., a C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.), an acyl group derived from a carboxylic acid (e.g., a C₁₋₆ alkanoyl such as formyl, acetyl, propionyl, pivaloyl, etc.), a C₇₋₁₅ arylcarbonyl such as benzoyl, etc., an acyl group derived from a sulfonic acid (e.g., a C₁₋₆ alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), an optionally halogenated C₂₋₆ alkoxy carbonyl (e.g., trifluoromethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, trichloromethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.), etc. In addition, the "amino group" in the "amino group which may be substituted" may be substituted with an imido group which may be substituted (e.g., a C₁₋₆ alkylimido, formylimido, amidino, etc.), etc. Alternatively, two substituents of the amino group may form a cyclic amino group together with a nitrogen atom. Examples of said cyclic amino group include e.g. 3 to 8-membered (preferably 5 or 6-membered) cyclic amino group such as 1-azetidyl, 1-pyrrolidyl, 1-piperidyl, 4-morpholinyl, 1-piperazinyl and 1-piperazinyl which may have at the 4-position a lower alkyl group (e.g., a C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.), an aralkyl group (e.g. a C₇₋₁₀ aralkyl group such as benzyl, phenethyl, etc.), an aryl group (e.g. a C₆₋₁₀ aryl group such as phenyl, 1-naphthyl, 2-naphthyl, etc.), etc.

[0019] Examples of the "carbamoyl group which may be substituted" include unsubstituted carbamoyl, a N-mono-substituted carbamoyl group and a N,N-di-substituted carbamoyl group.

[0020] The "N-mono-substituted carbamoyl group" is a carbamoyl group having one substituent on the nitrogen atom and the substituent include, for example, a lower alkyl group (e.g., a C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.), a cycloalkyl group (e.g., a C₃₋₆ cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), an aryl group (e.g., a C₆₋₁₀ aryl group such as phenyl, 1-naphthyl, 2-naphthyl, etc.), an aralkyl group (e.g., a C₇₋₁₀ aralkyl group, preferably a phenyl-C₁₋₄ alkyl group such as benzyl, phenethyl, etc.), a heterocyclic group (e.g., the above described "heterocyclic group" as the substituent of the "hydrocarbon group which may be substituted" represented by R¹, etc.), etc. The lower alkyl group, the cycloalkyl group, the aryl group, the aralkyl group and the heterocyclic group as described above may have substituent(s), and the substituent(s) include, for example, a hydroxy group, an amino group which may be substituted [the amino group may have 1 or 2 substituent(s) (e.g. a lower alkyl group (e.g., a C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.), an acyl group (e.g., a C₁₋₆ alkanoyl such as formyl, acetyl, propionyl, pivaloyl, etc., an arylcarbonyl such as benzoyl, etc., a C₁₋₆ alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), etc.)], a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a nitro group, a cyano group, a lower alkyl group which may be substituted with 1 to 5 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine, etc.), a lower alkoxy group which may be substituted with 1 to 5 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine, etc.), etc. The lower alkyl group includes, e.g. a C₁₋₆ alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc. and in particular methyl, ethyl, etc. are preferable. Said lower alkoxy group include e.g. a C₁₋₆ alkoxy group such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc. and in particular methoxy, ethoxy, etc. are preferable. The above described lower alkyl group, cycloalkyl group, aryl group, aralkyl group and heterocyclic group may have 1, 2 or 3 (preferably 1 or 2) substituent(s).

[0021] The "N,N-di-substituted carbamoyl group" is a carbamoyl group having two substituents on the nitrogen atom. Examples of one of the substituents include the same as those of the above described "N-mono-substituted carbamoyl group" and examples of the other substituent include e.g. a lower alkyl group (e.g., a C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.), a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), a C₇₋₁₀ aralkyl group (e.g., benzyl, phenethyl, etc., preferably phenyl-C₁₋₄ alkyl group, etc.), etc. In addition, two substituents of the "N,N-di-substituted carbamoyl group" may form a cyclic amino group together with a nitrogen atom. Examples of said cyclic aminocarbonyl group include, e.g., 3 to 8-membered (preferably 5 or 6-membered) cyclic aminocarbonyl group such as 1-azetidylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, 4-morpholinylcarbonyl, 1-piperazinylcarbonyl and 1-piperazinylcarbonyl which may have a lower alkyl group (e.g., a

C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.), an aralkyl group (e.g., a C₇₋₁₀ aralkyl group such as benzyl, phenethyl, etc.), an aryl group (e.g., a C₆₋₁₀ aryl group such as phenyl, 1-naphthyl, 2-naphthyl, etc.), etc. at the 4-position.

[0022] Examples of the "sulfamoyl group which may be substituted" include an unsubstituted sulfamoyl group, a N-mono-substituted sulfamoyl group and a N,N-di-substituted sulfamoyl group.

[0023] The "N-mono-substituted sulfamoyl group" is a sulfamoyl group having one substituent at the nitrogen atom, and examples of the substituent include those mentioned for the substituents of N-mono-substituted carbamoyl group.

[0024] The "N,N-di-substituted sulfamoyl group" is a sulfamoyl group having two substituents at the nitrogen atom, and examples of the substituents include those mentioned as the substituents of the N,N-di-substituted carbamoyl group.

[0025] Examples of the "acyl group derived from a sulfonic acid" include a sulfonyl group substituted by a hydrocarbon group, and preferably, include an acyl group such as C₁₋₁₀ alkylsulfonyl, C₂₋₆ alkenylsulfonyl, C₂₋₆ alkynylsulfonyl, C₃₋₉ cycloalkylsulfonyl, C₃₋₉ cycloalkenylsulfonyl, C₆₋₁₄ arylsulfonyl, C₇₋₁₀ aralkylsulfonyl. Examples of the C₁₋₁₀ alkyl include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, etc. Examples of the C₂₋₆ alkenyl include, for example, vinyl, allyl, 1-propenyl, isopropenyl, 2-butenyl, 3-butenyl, 2-hexenyl, etc. Examples of C₂₋₆ alkynyl include, for example, ethynyl, 2-propynyl, 2-butylnyl, 5-hexynyl, etc. Examples of the C₃₋₉ cycloalkyl include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, etc. Examples of the C₃₋₉ cycloalkenyl include, for example, 1-cyclopenten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 3-cyclohexen-1-yl, 3-cycloocten-1-yl, etc. Examples of the C₆₋₁₄ aryl include, for example, phenyl, 1-naphthyl, 2-naphthyl, etc. Examples of the C₇₋₁₀ aralkylsulfonyl include, for example, benzyl, phenethyl, etc. These hydrocarbon groups which are the substituents of the sulfonyl may be substituted. Examples of these substituents include, for example, hydroxy group, amino group which may be substituted [(the amino group may be substituted by one or two C₁₋₆ alkyl(s) (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.), an acyl group (e.g.,

[0026] C₁₋₆ alkanoyl such as formyl, acetyl, propionyl, pivaloyl, etc., aryl carbonyl such as benzoyl, etc., C₁₋₆ alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, lower alkyl which may be substituted by 1 to 5 halogen atom(s) (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkoxy which may be substituted by 1 to 5 halogen atom(s) (e.g. fluorine, chlorine, bromine, iodine, etc.). Examples of the lower alkyl group include, for example, C₁₋₆ alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc., and preferably include methyl, ethyl, etc. The lower alkoxy group includes, for example, C₁₋₆ alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc. and preferably include methoxy, ethoxy, etc. Preferably, one, two or three (preferably one or two) from these substituents is(are) used, wherein the substituents may be the same or different.

[0027] "Cyclic hydrocarbon group" in the "cyclic hydrocarbon group which may be substituted" of R² include alicyclic hydrocarbon group and aryl group.

[0028] Examples of the "alicyclic hydrocarbon group" include, for example, a saturated or unsaturated alicyclic hydrocarbon group such as a cycloalkyl group, a cycloalkenyl group, a cycloalkanedienyl group, etc. Examples of the "cycloalkyl group" include, for example, a C₃₋₉ cycloalkyl (preferably, a C₃₋₈ cycloalkyl) such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, etc., and a fused ring such as 1-indanyl, 2-indanyl, etc. Examples of the "cycloalkenyl group" include, for example, a C₃₋₆ cycloalkenyl group such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 1-cyclobuten-1-yl, 1-cyclopenten-1-yl, etc. Examples of the "cycloalkanedienyl group" include, for example, a C₄₋₆ cycloalkanedienyl group such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl, etc. In particular, a C₃₋₈ cycloalkyl is preferable.

[0029] Examples of the "aryl group" exemplified by the hydrocarbon group include, for example, a monocyclic or fused aromatic hydrocarbon group. Among others, a C₆₋₁₄ aryl group such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, 4-indanyl, 5-indanyl, etc. are preferable. In particular, phenyl, 1-naphthyl, 2-naphthyl, etc. are preferable.

[0030] Examples of the "substituent(s)" in the "cyclic hydrocarbon group which may be substituted" represented by R² are those similar to the "substituent" of the "hydrocarbon group which may be substituted" described as the substituent(s) of the "hydrocarbon group which may be substituted", which are represented by R¹.

[0031] Examples of the "heterocyclic group which may be substituted" of R² are those similar to the "heterocyclic group which may be substituted" described as the substituent(s) of the "hydrocarbon group which may be substituted", which are represented by R¹.

[0032] The halogen atom represented by R³ include, for example, fluorine, chlorine, bromine, iodine, etc.

[0033] The "carbamoyl group which may be substituted", "sulfamoyl group which may be substituted" and "acyl group derived from a sulfonic acid" represented by R³ are those similar to the "carbamoyl group which may be substituted", "sulfamoyl group which may be substituted" and "acyl group derived from a sulfonic acid", which are represented by R¹.

[0034] Examples of the "C₁₋₄ alkyl group" of the "C₁₋₄ alkyl group which may be substituted" represented by R³ include, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl. Examples of the "C₁₋₄ alkoxy group"

of the "C₁₋₄ alkoxy group which may be substituted" represented R³ include, for example, methoxy, ethoxy, propoxy, n-butoxy, isobutoxy, tert-butoxy.

[0035] Example of the substituent(s) in the "C₁₋₄ alkyl group which may be substituted" and "C₁₋₄ alkoxy group which may be substituted", which is represented by R³ are those similar to the "substituent(s)" of the "hydrocarbon group which may be substituted" that is(are) the "substituent(s)" of "the hydrocarbon group which may be substituted", which is represented by R¹.

[0036] Examples of the substituents of "amino group which may be substituted" represented by R³ include, for example, lower alkyl group (e.g., C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.), an acyl group derived from carboxylic acid (e.g., C₁₋₆ alkanoyl such as formyl, acetyl, propionyl, pivaloyl, etc.), for example, C₇₋₁₅ arylcarbonyl such as benzoyl, etc., an acyl group derived from sulfonic acid (e.g., C₁₋₆ alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, etc.), an optionally halogenated C₁₋₆ alkoxy-carbonyl (e.g., trifluoromethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, trichloromethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.), etc. In addition, the "amino group" of the "amino group which may be substituted" may be substituted with an imido group which may be substituted (e.g., a C₁₋₆ alkylimido, formylimido, amidino, etc.), etc. and two substituents of the "amino group" may form a cyclic amino group together with a nitrogen atom. Examples of said cyclic amino group include, for example, 3 to 8-membered (preferably, 5 or 6-membered) cyclic amino group such as 1-azetidyl, 1-pyrrolidyl, 1-piperidyl, 4-morpholyl, 1-piperazyl and 1-piperazyl which may have a lower alkyl group (e.g., a C₁₋₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.), an aralkyl group (e.g., a C₇₋₁₀ aralkyl group such as benzyl, phenethyl, etc.), an aryl group (e.g., a C₆₋₁₀ aryl group such as phenyl, 1-naphthyl, 2-naphthyl, etc.), etc. at the 4-position.

[0037] Examples of the leaving group represented by X include, for example, a halogen atom (e.g., a chlorine atom, a bromine atom, an iodine atom, etc.), an alkyl or aryl sulfonyloxy group (e.g., methanesulfonyloxy, trifluoromethanesulfonyloxy, ethanesulfonyloxy, benzenesulfonyloxy, p-toluenesulfonyloxy, etc.), etc.

[0038] Examples of the salt of a compound of the formula (I) of the present invention include a salt with an acid, for example, a salt with inorganic acid (e.g., hydrochloric acid salt, sulfuric acid salt, hydrobromic acid salt, phosphoric acid salt, etc.), a salt of an organic acid (e.g., acetic acid salt, trifluoroacetic acid salt, succinic acid salt, maleic acid salt, fumaric acid salt, propionic acid salt, citric acid salt, tartaric acid salt, lactic acid salt, oxalic acid salt, methanesulfonic acid salt, p-toluenesulfonic acid salt, etc.), etc., a salt with a base (e.g., an alkali metal salt such as potassium salt, sodium salt, lithium salt, etc., an alkaline earth metal salt such as calcium salt, magnesium salt, etc., ammonium salt, a salt with an organic base such as trimethylamine salt, triethylamine salt, tert-butyl dimethyl amine salt, dibenzyl methylamine salt, benzyl dimethylamine salt, N,N-dimethylaniline salt, pyridine salt, quinoline salt, etc.).

[0039] The compound of the formula (I) or salt thereof may also be hydrated. Hereinafter the compound of the formula (I), its salt and its hydrate are referred to as Compound (I).

[0040] A prodrug of the Compound (I) of the present invention means a compound which is converted to the Compound (I) having inhibitory activity of CCR5 by a reaction due to an enzyme, a gastric acid, etc. in vivo.

[0041] Examples of the prodrug of the Compound (I) include a compound wherein an amino group of the Compound (I) is substituted with acyl, alkyl, phosphoric acid (e.g. a compound wherein an amino group of the Compound (I) is substituted with eicosanoyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuran-2-yl, pyrrolidinylmethyl, pivaloyloxymethyl, acetoxymethyl, tert-butyl, etc.); a compound wherein a hydroxy group of the Compound (I) is substituted with an acyl, an alkyl, a phosphoric acid group, a boric acid group (e.g. a compound wherein a hydroxy group of the Compound (I) is substituted with acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl, etc.); a compound wherein a carboxyl group of the Compound (I) is modified to ester, amide (e.g. a compound wherein a carboxyl group of the Compound (I) is modified to ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester, methyl amide, etc.); etc. These prodrugs can be produced by per se known method.

[0042] The prodrug of the Compound (I) may be a compound which is converted into the Compound (I) under the physiological conditions as described in "Pharmaceutical Research and Development", Vol. 7 (Drug Design), pages 163-198 published in 1990 by Hirokawa Publishing Co. (Tokyo, Japan).

[0043] The prodrug of the Compound (I) may be distinct entity or in the form of a pharmaceutically acceptable salts. Examples of said salt include a salt with an inorganic base (e.g., an alkaline metal such as sodium, potassium, etc.; an alkaline earth metal such as calcium, magnesium, etc.; transition metal such as zinc, iron, copper, etc.); an organic base (e.g., an organic amine such as trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.); a basic amino acid such as arginine, lysine, ornithine, etc.); etc., when the prodrug of the Compound (I) has an acidic group such as a carboxyl group, etc.

[0044] Examples of said salt also include a salt with an inorganic acid or an organic acid (e.g., hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, carbonic acid, bicarbonic acid, formic acid, acetic acid, propionic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesul-

[0053] In the above formula, each symbol has the same meaning as defined above.

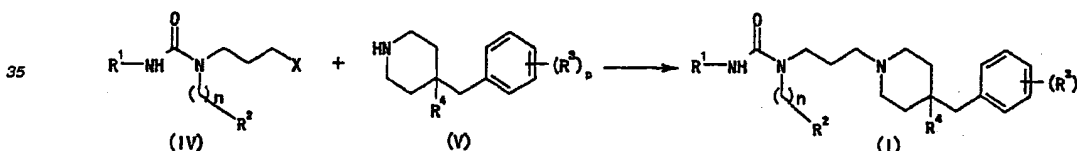
[0054] The compound can be produced by reacting acrolein (VI) with Compound (V), followed by reacting the resulting compound with Compound (VIII) under a condition of reduction. The reaction of Compound (VI) with Compound (V) is usually carried out in a solvent inert to the reaction in the presence of a base. Examples of the base include 1) a strong base such as hydride of alkali metal or alkaline earth metal (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride, etc.), an amide of an alkali metal or an alkaline earth metal (e.g., lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, etc.), a lower alkoxide of alkali metal or alkaline earth metal (e.g., sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), etc., 2) an inorganic base such as a hydroxide of an alkali metal or an alkaline earth metal (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, etc.), a carbonate of an alkali metal or an alkaline earth metal (e.g., sodium carbonate, potassium carbonate, cesium carbonate, etc.), a bicarbonate of alkali metal or alkaline earth metal (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), etc., 3) an organic base, etc., such as an amine as triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]-7-undecene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), etc., and such basic heterocyclic Compound, etc., as pyridine, imidazole, 2,6-lutidine, etc. Examples of the solvent include those mentioned in the reaction of Compound (II) with Compound (III). These solvents can be used solely or in combination. Compound (VII) can be obtained in the reaction.

[0055] Examples of the reducing agent for the reaction of Compound (VII) with Compound (VIII) include sodium borohydride, lithium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, etc. The used amount of the reducing agent is usually in the range of 1 to 10 equivalents, preferably in the range of 1 to 4 equivalents relative to 1 equivalent of Compound (VII). The reaction temperature ranges -20 to 50°C, preferably 0°C to room temperature, and reaction time is 0.5 to 24 hours.

[0056] Catalytic reduction reaction is carried out in the presence of a catalytic amount of a metal catalyst such as Raney nickel, platinum oxide, metallic palladium, palladium-carbon, etc., in an inert solvent (e.g., an alcohol such as methanol, ethanol, isopropanol, t-butanol, etc.), at room temperature to 100°C, under a hydrogen pressure of 1 to 100 atm for 1 to 48 hours.

Production 2

30 **[0057]** Compound (I) can be produced by reacting Compound (IV) with Compound (V) as shown below.



⁴⁰ (In the above formulas, each symbol has the same meaning as defined above.)

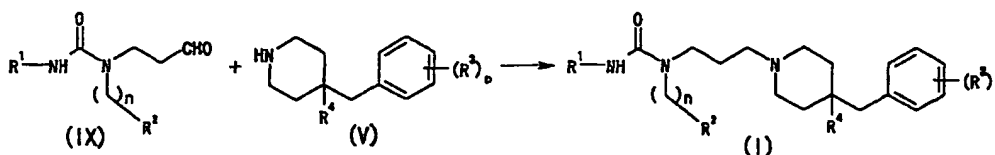
[0058] The reaction can be carried out by a manner similar to that described in Organic Functional Group Preparations 2nd ed., (Academic Press, Inc.).

[0059] The reaction is usually carried out in a solvent inert to the reaction. Examples of the solvent include an alcohol, an ether, a halogen solvent, an aromatic solvent, acetonitrile, N,N-dimethylformamide (DMF), acetone, methylethyl ketone, dimethylsulfoxide (DMSO), etc. These solvents can be used solely or in combination. Among them, acetonitrile, dimethylformamide, acetone, ethanol, etc., are preferable. The reaction temperature ranges usually from room temperature to 100°C, preferably from room temperature to 50°C, and the reaction time is usually 0.5 to 1 day. In this reaction, a base is usually added in an amount of 1 to 3 equivalents relative to 1 equivalent of Compound (IV), but it is not essential. Examples of the base include those mentioned in the reaction of Compound (II) with Compound (III).

50 **[0060]** Compound (IV) used as a starting material in the reaction can be produced from Compound (III) by a known conventional method.

Production 3

55 **[0061]** Compound (I) can be produced by reacting a compound of the formula (IX) with a compound of the formula (V) under a reduction condition as shown below.



(In the above formulas, each symbol has the same meaning as defined above.)

[0062] The reaction is carried out by reacting Compound (IX) with Compound (V) in an appropriate solvent (e.g., water, an alcohol, an ether, a halogenated solvent, acetonitrile, or a mixed solvent of two or more of these solvents, etc.), if necessary, by the addition of acidic substance such as acetic acid, trifluoroacetic acid, etc., in the presence of 1 to 5 equivalents, preferably 1 to 1.5 equivalent of a reducing agent. The reducing agent and the reaction condition mentioned in Production 1 can be applied for this reaction.

[0063] Compound (IX) used as a starting material in the reaction can be produced from Compound (III) by a known conventional method.

[0064] The Compound (I) of the present invention has potent CCR antagonistic activity (in particular, potent CCR5 antagonistic activity) and therefore can be used for the treatment or prevention of various infectious diseases of HIV in human, for example, AIDS. The compound (I) of the present invention is low toxic and safely used.

[0065] The Compound (I) of the present invention can be used as a CCR5 antagonist, for example, a drug for treatment or prevention of AIDS or a drug for the prevention of the progression of AIDS.

[0066] The compound of the present invention can be formulated by mixing individually or simultaneously with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, which can be administered orally or non-orally as a pharmaceutical composition. It is well absorbed by orally. It can be administrated as tablets, capsules, granules and powders.

[0067] The dose per day of the compound (I) varies depending on the condition and body weight of a patient, administration route, etc. Typical daily dose per adult patient (body weight: 50 Kg) for oral administration is about 5 to 1000 mg, preferably about 10 to 600 mg, more preferably about 10 to 300 mg, and in particular about 15 to 150 mg, as an active ingredient [the compound (I)] and the compound (I) is administered once or 2 to 3 times per day.

[0068] The compound (I) of the present invention may be used in combination with other drugs for the treatment or prevention of infectious disease of HIV (in particular, a drug for the treatment or prevention of AIDS). In this case, these drugs can be formulated by mixing individually or simultaneously with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, which can be administered orally or non-orally as a pharmaceutical composition for the treatment or prevention of infectious disease of HIV. In the case of formulating these effective components individually, while the individually formulated agents can be administered in the form of their mixture prepared by using e.g. a diluent when administered, the individually formulated agents can also be administered separately or simultaneously or with time intervals to the one and same subject. A kit for administering the individually formulated effective components in the form of their mixture prepared by using e.g. a diluent when administered (e.g. a kit for injection which comprises two or more ampoules each comprising a powdery component and a diluent for mixing and dissolving two or more components when administered, etc.), a kit for administering the individually formulated agents simultaneously or with time intervals to the one and the same subject (e.g. a kit for tablets to be administered simultaneously or with time intervals, characterized by having two or more tablets each comprising an agent and said tablets being put in one or separate bags and, if necessary, a column to describe time to be administered each agent, etc.), etc. are also included by the pharmaceutical composition of the present invention.

[0069] Example of the other pharmaceutical agent for the treatment or prevention of infectious disease of HIV to be used in combination with the compound (I) of the present invention include nucleoside reverse transcriptase inhibitor such as zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, adefovir, adefovir dipivoxil, fozivudine tidoxil, etc.; non-nucleoside reverse transcriptase inhibitor (including an agent having anti-oxidative activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, etc.; protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, palinavir, lasinavir, etc.; etc.

[0070] As the nucleoside reverse transcriptase inhibitor, zidovudine, didanosine, zalcitabine, lamivudine, stavudine, etc. are preferable; as the non-nucleoside reverse transcriptase inhibitor, nevirapine, delavirdine, etc. are preferable; and as the protease inhibitor, saquinavir, ritonavir, indinavir, nelfinavir, etc. are preferable.

[0071] The compound (I) of the present invention may be used in combination with, for example, CXCR4 antagonist (CXCR4 being a second receptor of T cell-tropic HIV-1) such as AMD-3100, etc., an antibody against HIV-1 surface antigen, HIV-1 vaccine, etc., in addition to the above-mentioned protease inhibitor, reverse transcriptase inhibitor, etc.

[0072] When the compound (I) is used in combination with a reverse transcriptase inhibitor and/or a protease inhibitor, the dose of the reverse transcriptase inhibitor or the protease inhibitor ranges, for example, from about 1/200 to 1/2

or more of usual dose to about 2 to 3 times or less of usual dose. In case that two or more drugs are used in combination, each dose of the drugs is appropriately adjusted if one drug affects metabolism of the other drug, while each dose of the drugs when they are used in combination is generally the same as the dose when they are used alone.

[0073] Typical daily dose of the reverse transcriptase inhibitor and the protease inhibitor is as follows:

5	zidovudine :	100 mg
	didanosine :	125 to 200 mg
	zalcitabine :	0.75 mg
	lamivudine :	150 mg
10	stavudine :	30 to 40 mg
	saquinavir :	600 mg
	ritonavir :	600 mg
	indinavir :	800 mg
	nelfinavir :	750 mg

15

[0074] In case of combination use of the compound (I) with a reverse transcriptase inhibitor and/or a protease inhibitor preferred embodiments are shown below.

20 (i) A drug containing about 10 to 300 mg of the compound (I) and a drug containing about 50 to 200 mg of zidovudine to one adult patient (body weight: 50 Kg) are administered. Each of the drugs may be administered to the one and the same subject simultaneously or with time intervals of 12 hours or less.

(ii) A drug containing about 10 to 300 mg of the compound (I) and a drug containing about 300 to 1200 mg of saquinavir to one adult patient (body weight: 50 Kg) are administered. Each of the drugs may be administered to the one and the same subject simultaneously or with time intervals of 12 hours or less.

25

BEST MODE FOR CARRYING OUT THE INVENTION

[0075] The present invention is hereinafter described in more detail by means of the following Example, Reference Example, Test Example and Formulation Example, which are mere examples of the present invention and are not construed as limitative to the present invention.

30 [0076] The following gene manipulation is carried out in accordance with methods described in textbook (Maniatis et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989) or protocol attached to reagents.

[0077] In the following Reference Examples and Examples, silica gel 60 (Merck, 70-230 or 230-400 mesh) was used as packing for column chromatography. Melting point was measured by using Yanaco MP-J3.

35 [0078] ¹H NMR spectra were measured using tetramethylsilane as an internal standard with a Gemini 200 spectrometer (Varian, 200 MHz). Mass spectrum (APCI-MS) was measured by using Platform II (Micromass).

[0079] Preparative HPLC was conducted under the following condition.

40 Instrument: combinatorial chromatography system (Gilson) Column: YMC CombiPrep ODS-A, 50×20 mm, S-5 μm
Eluant: A) 0.1% solution of trifluoroacetic acid in water, B) 0.1% solution of trifluoroacetic acid in acetonitrile 0.00 min (A/B = 90/10), 1.20 min (A/B = 90/10), 4.40 min (A/B = 0/100), 5.60 min (A/B = 0/100)
Amount injected: 500 μl, Flow Rate: 25 ml/min,
Detection: UV 220 nm

45 [0080] HPLC analysis was conducted under the following condition.

Instrument: LC-10Avp system (Shimadzu)
Column: CAPCELL PAK C18 UG120, 50 x 2.0 mm, S-3 μm
Eluant: A) 0.1% solution of trifluoroacetic acid in water, B) 0.1% solution of trifluoroacetic acid in acetonitrile 0.00 min (A/B = 90/10), 4.00 min (A/B = 5/95), 5.50 min (A/B = 5/95), 5.51 min (A/B = 90/10), 8.00 min (A/B = 90/10)
50 Flow Rate: 0.5 ml/min, Detection: UV 220 nm

Reference Example 1

55 N-[3-(4-Benzyl-1-piperidiny)propyl]aniline dihydrochloride

[0081] A solution of acrolein (90%, 18.69 g, 300 mmol) in THF (60 ml) was dropwise added to a solution of 4-benzylpiperidine (52.58 g, 300 mmol) and DBU (0.449 ml, 3.0 mmol) in THF (600 ml) for 10 minutes at -20°C under stirring.

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The mixture was stirred for 1 hour raising the temperature from -20°C to -10°C. Aniline (27.94 g, 300 mmol) and triacetoxysodium borohydride (127.16 g, 600 mmol) were added to the reaction mixture successively at -10°C. The mixture was stirred for 19 hours raising the temperature to room temperature. An aqueous solution of 2N sodium hydroxide (900 ml) was added to the reaction mixture under ice cooling, and the mixture was stirred for 30 minutes and extracted with diethyl ether (400 ml, 200 ml×2). The organic phase was dried over magnesium sulfate (anhydrous) and concentrated under reduced pressure. The residue was dissolved in 2-propanol (400 ml), and 4N hydrogen chloride in ethyl acetate (200 ml) was added to the solution with stirring. The resulting precipitate was collected by filtration. The precipitate was washed with 2-propanol (100 ml×3) and dried under reduced pressure to obtain the title compound as a white crystal (75.66 g, 198 mmol). Yield 66%. Melting Point 217°C (dec.)

¹H NMR (DMSO-d₆) δ 1.4-1.9 (5H, m), 2.0-2.25 (2H, m), 2.45-2.6 (2H, m), 2.83 (2H, br t, J=11.4Hz), 3.12 (2H, br t, J=7.2Hz), 3.29 (2H, br t, J=6.9Hz), 3.41 (2H, br d, J=12.6Hz), 7.05-7.5 (10H, m)

Anal. Calcd for C₂₁H₂₈N₂ • 2HCl • 0.5H₂O: C, 64.61; H, 8.00; N, 7.18. Found: C, 64.71; H, 7.92; N, 7.32.

Free base (N-[3-(4-benzyl-1-piperidiny)propyl]aniline)

¹H NMR (CDCl₃) δ 1.05-1.85 (9H, m), 2.34 (2H, t, J=6.8Hz), 2.46 (2H, d, J=6.6Hz), 2.83 (2H, br d, J=11.8Hz), 3.06 (2H, t, J=6.4Hz), 6.45-6.65 (3H, m), 7.0-7.25 (7H, m)

Reference Example 2

N-[3-(4-Benzyl-1-piperidiny)propyl]-3-chloroaniline dihydrochloride

[0082] Using 3-chloroaniline, the title compound was synthesized in a manner similar to Reference Example 1. Yield 41%.

Melting Point 202°C (dec.)

¹H NMR (DMSO-d₆) δ 1.53-2.01 (7H, m), 2.50-2.55 (2H, m), 2.66-2.92 (2H, m), 3.08-3.20 (4H, m), 3.38-3.44 (2H, m), 6.61-6.69 (3H, m), 7.07-7.30 (6H, m)

Anal. Calcd for C₂₁H₂₇ClN₂ • 2HCl • 0.1H₂O: C, 60.39; H, 7.04; N, 6.71. Found: C, 60.33; H, 6.93; N, 6.84.

Reference Example 3

N-[3-(4-Benzyl-1-piperidiny)propyl]-3,4-dichloroaniline dihydrochloride

[0083] Using 3,4-dichloroaniline, the title compound was synthesized in a manner similar to Reference Example 1. Yield 53%.

Melting Point 203°C (dec.)

¹H NMR (DMSO-d₆) δ 1.49-1.76 (5H, m), 1.91-1.96 (2H, m), 2.50-2.55 (2H, m), 2.79-3.17 (6H, m), 3.38-3.44 (2H, m), 6.68 (1H, dd, J=2.8, 8.8Hz), 6.75 (1H, d, J=2.6Hz), 7.17-7.30 (6H, m) Anal. Calcd for C₂₁H₂₆Cl₂N₂ • 2HCl • 0.5H₂O: C, 54.92; H, 6.36; N, 6.10. Found: C, 55.11; H, 6.64; N, 6.37.

Reference Example 4

N-[3-(4-Benzyl-1-piperidiny)propyl]-4-methylaniline dihydrochloride

[0084] Using p-toluidine, the title compound was synthesized in a manner similar to Reference Example 1. Yield 57%. Melting Point 182-192°C (dec.)

¹H NMR (DMSO-d₆) δ 1.4-1.9 (5H, m), 2.0-2.25 (2H, m), 2.31 (3H, s), 2.45-2.6 (2H, m), 2.7-2.95 (2H, m), 2.95-3.55 (6H, m), 7.1-7.45 (9H, m)

Anal. Calcd for C₂₂H₃₀N₂ • 2HCl • 0.5H₂O: C, 65.34; H, 8.22; Cl, 17.53; N, 6.93. Found: C, 65.24; H, 8.38; Cl, 17.37; N, 6.98.

Reference Example 5-1

4-(4-Fluorobenzyl)piperidine hydrochloride

[0085] 4-Fluorobenzylbromide (100 g) and triethyl phosphite (120 ml) were mixed and the mixture was stirred for 22 hours at 150°C. The obtained reaction mixture was distilled under reduced pressure (bp 115-120°C/1.5 mmHg) to give diethyl 4-fluorobenzyl phosphonate (125 g).

[0086] 60% Sodium hydride (oily, 9.75 g) was added to a solution of diethyl 4-fluorobenzyl phosphonate (60.8 g) and 15-crown-5 (4 ml) in THF (400 ml) with stirring under ice cooling, and the mixture was stirred for 30 minutes at the

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same temperature. A solution of 1-tert-butoxycarbonyl-4-piperidone (42.0 g) in THF (150 ml) was dropwise added to the mixture with stirring under ice cooling, and the mixture was stirred for 22 hours at room temperature. Under ice cooling, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated aqueous solutions of sodium bicarbonate and saturated brine in order. The organic phase was dried over magnesium sulfate (anhydrous) and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel 650 g, hexane/ethyl acetate=30/1→10/1). The objective fraction was concentrated under reduced pressure to give 1-tert-butoxycarbonyl-4-(4-fluorobenzylidene)piperidine (47.0 g).

¹H NMR (CDCl₃) δ 1.48 (9H, s), 2.32-2.44 (4H, m), 3.37-3.53 (4H, m), 6.31 (1H, s), 7.00-7.19 (4H, m)

[0087] 1-tert-Butoxycarbonyl-4-(4-fluorobenzylidene)piperidine (47.0 g) was dissolved in methanol (450 ml). 10% Palladium carbon (containing 50% water, 4.7 g) was added to the solution and the mixture was subjected to catalytic hydrogenation for 5 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 1-tert-butoxycarbonyl-4-(4-fluorobenzyl)piperidine (39.9 g).

¹H NMR (CDCl₃) δ 1.08-1.64 (14H, m), 2.49-2.69 (4H, m), 4.04-4.10 (2H, m), 6.92-7.12 (4H, m)

[0088] A solution of 4N hydrogen chloride in ethyl acetate (100 ml) was added to 1-tert-butoxycarbonyl-4-(4-fluorobenzyl)piperidine (39.9 g) and the solution was stirred for an hour at room temperature. The reaction mixture was concentrated under reduced pressure, then diethyl ether was added thereto. The resulting precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give the title compound (30.1 g).

¹H NMR (CDCl₃) δ 1.70-1.81 (5H, m), 2.52-2.59 (2H, m), 2.71-2.89 (2H, m), 3.42-3.59 (2H, m), 6.93-7.07 (4H, m)

20 Reference Example 5-2

4-(4-Fluorobenzyl)piperidine

[0089] An aqueous solution of 1N sodium hydroxide (66 ml) was added to the compound obtained in Reference Example 5-1 (5.05 g), and the mixture was extracted with diethyl ether. The organic phase was dried over magnesium sulfate (anhydrous) and concentrated under reduced pressure to give the title compound.

¹H NMR (CDCl₃) δ 1.0-1.35 (2H, m), 1.35-1.7 (3H, m), 2.45-2.65 (2H, m), 2.49 (2H, d, J=6.6Hz), 2.95-3.1 (2H, m), 6.95 (2H, t, J=8.8Hz), 7.0-7.15 (2H, m)

30 Reference Example 5-3

N-[3-[4-(4-Fluorobenzyl)-1-piperidinyl]propyl]aniline dihydrochloride

[0090] Using the compound obtained in Reference Example 5-2, the title compound was obtained in a manner similar to Reference Example 1. Yield 54%.

Melting Point 230°C (dec.)

¹H NMR (DMSO-d₆) δ 1.35-1.9 (5H, m), 1.95-2.2 (2H, m), 2.45-2.6 (2H, m), 2.83 (2H, br t, J=11.5Hz), 3.11 (2H, br t, J=7.4Hz), 3.24 (2H, br t, J=6.8Hz), 3.42 (2H, br d, J=10.6Hz), 6.9-7.2 (9H, m)

40 Reference Example 6

3,4-Dichloro-N-[3-[4-(4-fluorobenzyl)-1-piperidinyl]propyl]aniline dihydrochloride

[0091] Using the compound obtained in Reference Example 5-2 and 3,4-dichloroaniline, the title compound was obtained in a manner similar to Reference Example 1. Yield 48%.

Melting Point 203-209°C (dec.)

¹H NMR (DMSO-d₆) δ 1.35-2.05 (7H, m), 2.45-2.6 (2H, m), 2.6-3.3 (6H, m), 3.41 (2H, br d, J=10.6Hz), 6.57 (1H, dd, J=2.7, 8.8Hz), 6.75 (1H, d, J=2.7Hz), 7.05-7.3 (5H, m)

Anal. Calcd for C₂₁H₂₅Cl₂FN₂ • 2HCl • 0.5H₂O: C, 52.85; H, 5.91; N, 5.87. Found: C, 52.90; H, 6.12; N, 5.94.

50 Reference Example 7

N-[3-(4-Benzyl-1-piperidinyl)propyl]benzylamine

[0092] A solution of acrolein (90%, 3.2 g, 57 mmol) in THF (2 ml) was dropwise added to a solution of 4-benzylpiperidine (10.0 g, 57 mmol) and DBU (85 μl, 0.57 mmol) in THF (10 ml) for 10 minutes at -20°C under stirring. The mixture was stirred for an hour raising the temperature from -20°C to -10°C.

[0093] Benzylamine (6.1 g, 57 mmol) and triacetoxy sodium borohydride (24.2 g, 114 mmol) were added to the

reaction mixture successively at -10°C, and the mixture was stirred for 19 hours raising the temperature to room temperature. An aqueous solution of 2N sodium hydroxide (100 ml) was added to the reaction mixture under ice cooling and the mixture was stirred for 30 minutes, and extracted with diethyl ether (100 ml, 80 ml×2). The organic phase was dried over magnesium sulfate (anhydrous), then concentrated under reduced pressure. The residue was dissolved in 2-propanol (50 ml) and to the solution was added a solution of 4N hydrogen chloride in ethyl acetate (50 ml) with stirring. The resulting precipitate was collected by filtration. The precipitate was washed with 2-propanol (20 ml×3) and dried under reduced pressure to give the title compound as a white crystal (6.5 g).

[0094] To the obtained white crystal (2.0 g) was added an aqueous solution of 1N sodium hydroxide (10 ml) to dissolve the crystal, and the solution was extracted with ethyl acetate (10 ml, 8 ml×2). The organic phase was dried over magnesium sulfate (anhydride) and concentrated under reduced pressure to give the title compound (1.6 g) as a colorless oil.

¹H NMR (CDCl₃) δ 1.30(2H, dt, J = 11.8 Hz, 2.4 Hz), 1.49(1H, m), 1.59-1.89(6H, m), 2.35(2H, t, J = 7.8 Hz), 2.52(2H, d, J = 6.8 Hz), 2.66(2H, t, J = 6.8 Hz), 2.90 (2H, d, J = 11.8 Hz), 3.78(2H, s), 7.12-7.33(10H, m)

MS (APCI⁺) 323 (M+1)

Reference Example 8

N-[3-(4-Benzyl-1-piperidiny)propyl]-4-fluorobenzylamine

[0095] Using 4-fluorobenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.

¹H NMR (CDCl₃) δ 1.26(2H, dt, J = 12.0 Hz, 2.6 Hz), 1.51(1H, m), 1.59-1.92(6H, m), 2.39(2H, t, J = 7.0 Hz), 2.49(2H, d, J = 6.8 Hz), 2.66(2H, t, J = 7.0 Hz), 2.91(2H, d, J = 11.8 Hz), 3.74(2H, s), 6.94-7.32(9H, m)

MS (APCI⁺) 341 (M+1)

Reference Example 9

N-[3-(4-Benzyl-1-piperidiny)propyl]-3-chlorobenzylamine

[0096] Using 3-chlorobenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.

¹H NMR (CDCl₃) δ 1.29(2H, dt, J = 12.0 Hz, 3.6 Hz), 1.41-1.91(7H, m), 2.38(2H, t, J = 7.6 Hz), 2.51(2H, d, J = 6.6 Hz), 2.67(2H, t, J = 6.6 Hz), 2.92(2H, d, J = 11.6 Hz), 3.76(2H, s), 7.11-7.33(9H, m)

MS (APCI⁺) 357 (M+1)

Reference Example 10

N-[3-(4-Benzyl-1-piperidiny)propyl]-3,4-dichlorobenzylamine

[0097] Using 3,4-dichlorobenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.

¹H NMR (CDCl₃) δ 1.29(2H, dt, J = 12.0 Hz, 2.6 Hz), 1.52(1H, m), 1.60-1.92(6H, m), 2.39(2H, t, J = 7.4 Hz), 2.51(2H, d, J = 6.8 Hz), 2.65(2H, t, J = 7.4 Hz), 2.92(2H, d, J = 11.8 Hz), 3.73(2H, s), 7.10-7.43(8H, m)

MS (APCI⁺) 391 (M+1)

Reference Example 11

N-[3-(4-Benzyl-1-piperidiny)propyl]-2,6-difluorobenzylamine

[0098] Using 2,6-difluorobenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.

¹H NMR (CDCl₃) δ 1.24(2H, dt, J = 12.0 Hz, 2.6 Hz), 1.52(1H, m), 1.55-1.90(6H, m), 2.42(2H, t, J = 7.0 Hz), 2.52(2H, d, J = 6.8 Hz), 2.69(2H, t, J = 7.0 Hz), 2.94(2H, d, J = 11.8 Hz), 3.76(2H, s), 6.91-7.38(8H, m)

MS (APCI⁺) 359 (M+1)

Reference Example 12

N-[3-(4-Benzyl-1-piperidiny)propyl]-2-chlorobenzylamine

[0099] Using 2-chlorobenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.

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¹H NMR (CDCl₃) δ 1.23(2H, dt, J = 11.8 Hz, 2.6 Hz), 1.52(1H, m), 1.57-1.89(6H, m), 2.37(2H, t, J = 7.0 Hz), 2.48(2H, d, J = 6.8 Hz), 2.63(2H, t, J = 7.0 Hz), 2.91(2H, d, J = 11.8 Hz), 3.72(2H, s), 6.95-7.40(9H, m)
MS (APCI⁺) 357 (M+1)

5 Reference Example 13

N-[3-(4-Benzyl-1-piperidiny)propyl]-4-chlorobenzylamine

[0100] Using 4-chlorobenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.
10 ¹H NMR (CDCl₃) δ 1.26(2H, dt, J = 12.0 Hz, 2.8 Hz), 1.51(1H, m), 1.59-1.90(6H, m), 2.39(2H, t, J = 7.0 Hz), 2.51(2H, d, J = 6.8 Hz), 2.66(2H, t, J = 7.0 Hz), 2.93(2H, d, J = 11.8 Hz), 3.72(2H, s), 6.95-7.33(9H, m)
MS (APCI⁺) 357 (M+1)

15 Reference Example 14

N-[3-(4-Benzyl-1-piperidiny)propyl]-4-methylbenzylamine

[0101] Using 4-methylbenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.
20 ¹H NMR (CDCl₃) δ 1.33 (2H, dt, J = 12.2 Hz, 2.6 Hz), 1.52(1H, m), 1.56-1.84(6H, m), 2.25(3H, s), 2.39(2H, t, J = 7.6 Hz), 2.52(2H, d, J = 6.8 Hz), 2.70(2H, t, J = 7.0 Hz), 2.90(2H, d, J = 11.8 Hz), 3.78(2H, s), 7.15-7.35(9H, m)
MS (APCI⁺) 337 (M+1)

Reference Example 15

25 N-[3-(4-Benzyl-1-piperidiny)propyl]-4-methoxybenzylamine

[0102] Using 4-methoxybenzylamine, the title compound was synthesized in a manner similar to Reference Example 7.
30 ¹H NMR (CDCl₃) δ 1.33(2H, dt, J = 12.2 Hz, 2.6 Hz), 1.52(1H, m), 1.56-1.91(6H, m), 2.39(2H, t, J = 7.8 Hz), 2.48(2H, d, J = 6.8 Hz), 2.69(2H, t, J = 6.8 Hz), 2.91(2H, d, J = 11.8 Hz), 3.80(2H, s), 3.94(3H, s), 7.12-7.47(9H, m)
MS (APCI⁺) 353 (M+1)

Reference Example 16

35 N-[3-(4-Benzyl-1-piperidiny)propyl](cyclohexylmethyl)amine

[0103] Using (cyclohexylmethyl)amine, the title compound was synthesized in a manner similar to Reference Example 7.
40 ¹H NMR (CDCl₃) δ 0.90(2H, t, J = 10.4 Hz), 1.17-1.30(7H, m), 1.53-1.94(11H, m), 2.35(2H, t, J = 7.8 Hz), 2.50-2.53(4H, m), 2.66(2H, t, J = 6.8 Hz), 2.90(2H, d, J = 11.8 Hz), 7.09-7.21(5H, m)
MS (APCI⁺) 329 (M+1)

Reference Example 17

45 N-[3-(4-Benzyl-1-piperidiny)propyl](3-pyridylmethyl)amine

[0104] Using 3-(aminomethyl)pyridine, the title compound was synthesized in a manner similar to Reference Example 7.
50 ¹H NMR (CDCl₃) δ 1.30(2H, dt, J = 11.8 Hz, 2.4 Hz), 1.49(1H, m), 1.51-1.95(6H, m), 2.39(2H, t, J = 7.8 Hz), 2.54(2H, d, J = 7.2 Hz), 2.69(2H, t, J = 7.0 Hz), 2.92(2H, d, J = 12.2 Hz), 3.79(2H, s), 7.15-7.19(7H, m), 8.25(1H, d, J = 2.0 Hz), 8.54(1H, d, J = 1.8 Hz)
MS (APCI⁺) 324 (M+1)

Reference Example 18-1

55

4-[[1-(Trifluoroacetyl)-4-piperidiny]methyl]benzenesulfonyl chloride

[0105] To the mixture of 1-(trifluoroacetyl)-4-benzylpiperidine (29.2 g, 108 mmol) and methylene chloride (10 ml) was

dropwise added chlorosulfonic acid (36 ml, 539 mmol) at -10°C for an hour. The mixture was stirred at 0°C for an hour and then stirred at room temperature for an hour. The reaction mixture was poured into ice-cooled water (500 ml) and extracted with methylene chloride (200 ml x 2). The extract was washed with an aqueous solution of 5% sodium bicarbonate (500 ml) and saturated brine (500 ml) successively. The organic phase was dried over magnesium sulfate (anhydrous), then concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 100 g, ethyl acetate/hexane= 1/20→1/5) to give the title compound as a colorless powdery crystal (16.5 g, 41%).

¹H NMR (CDCl₃) δ 1.26-1.39 (2H, m), 1.75-2.05 (3H, m), 2.66-2.78 (1H, m), 2.48 (2H, d, J = 7.0Hz), 3.01-3.15 (1H, m), 3.98-4.10 (1H, m), 4.50-4.61 (1H, m), 7.40 (2H, d, J = 8.4Hz), 7.98 (2H, d, J = 8.4Hz)

Reference Example 18-2

4-[(4-[(1-(Trifluoroacetyl)-4-piperidiny]methyl)phenyl)sulfonyl]morpholine

[0106] Morpholine (0.88 ml, 10.1 mmol) was added to a solution of the compound obtained in Reference Example 18-1 (1.5 g, 4.1 mmol) in THF (10 ml) at 0°C. The mixture was stirred for an hour. The obtained reaction solution was diluted by 1N hydrochloric acid, and extracted with ethyl acetate (50 ml). The organic phase was washed with saturated brine (50 ml) and dried over sodium sulfate (anhydrous). The solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give (silica gel 20 g, ethyl acetate/hexane = 1/5→1/1) the title compound (1.37 g, 80%) as a pale yellow oil.

¹H NMR (CDCl₃) δ 1.17-1.38 (2H, m), 1.73-1.94 (3H, m), 2.66 (2H, d, J = 7.0Hz), 2.68-2.78 (1H, m), 3.00 (4H, t, J = 4.8Hz), 3.01-3.15 (1H, m), 3.76 (4H, t, J = 4.8Hz), 3.98-4.10 (1H, m), 4.53-4.60 (1H, m), 7.33 (2H, d, J = 8.4Hz), 7.69 (2H, d, J = 8.4Hz)

Reference Example 18-3

4-[(4-(4-Piperidiny)methyl)phenyl)sulfonyl]morpholine

[0107] The mixture of the compound obtained in Reference Example 18-2 (1.3 g, 3 mmol), an aqueous solution of 1M potassium carbonate (10 ml) and methanol (20 ml) was stirred at room temperature for 5 hours. Saturated brine (20 ml) was added to the mixture, and the mixture was extracted with methylene chloride (20 ml→2) and diethyl ether (20 ml) successively.

The extract was dried over magnesium sulfate (anhydrous). The solvent was removed under reduced pressure to give the title compound as a colorless powdery crystal (937 mg, 48%).

¹H NMR (CDCl₃) δ 1.21-1.82 (5H, m), 2.60-2.71 (4H, m), 3.00 (4H, t, J = 4.8Hz), 3.19-3.26 (2H, m), 3.75 (4H, t, J = 4.8Hz), 5.08 (1H, brs), 7.32 (2H, d, J = 8.4Hz), 7.67 (2H, d, J = 8.4Hz)

Reference Example 18-4

N-(3-[4-[4-(4-Morpholinyl)sulfonyl]benzyl]-1-piperidiny]propyl)aniline dihydrochloride

[0108] Using the compound obtained in Reference Example 18-3, the title compound was obtained in a manner similar to Reference Example 1. Yield 30%.

Free base: ¹H NMR (CDCl₃) δ 1.23 - 2.10 (9H, m), 2.47 (2H, t, J = 6.4 Hz), 2.64 (2H, t, J = 6.4 Hz), 2.89-3.06 (6H, m), 3.17 (2H, t, J = 6.4 Hz), 3.68-3.80 (4H, m), 6.57-6.72 (3H, m), 7.14-7.22 (2H, m), 7.33 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz)

Reference Example 19-1

4-[(1-Acetyl-4-piperidiny)methyl]benzenesulfonyl chloride

[0109] To chlorosulfonic acid (92 mL), a solution of 1-acetyl-4-benzylpiperidine (60.00 g) in dichloromethane (100 mL) was dropwise added for an hour at 0°C under stirring, and the mixture was stirred at 0°C for 30 minutes and at room temperature for 1.5 hours. The reaction mixture was poured into ice-cooled water (1 L) and extracted with dichloromethane (500 mL, 250 mL). The organic phase was washed with an aqueous solution of 5% sodium carbonate (500 mL x 2) and saturated brine (250 mL). The organic phase was dried over magnesium sulfate (anhydrous), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel 250 g, ethyl acetate). The objective fraction was concentrated under reduced pressure to give the title compound as a white solid

(54.22 g).

¹H NMR (CDCl₃) δ 1.05-1.35 (2H, m), 1.6-1.95 (3H, m), 2.09 (3H, s), 2.35-2.65 (1H, m), 2.68 (2H, d, J=6.6Hz), 2.85-3.15 (1H, m), 3.7-3.9 (1H, m), 4.5-4.75 (1H, m), 7.39 (2H, d, J=8.4Hz), 7.97 (2H, d, J=8.4Hz)

5 Reference Example 19-2

1-Acetyl-4-[4-(methylsulfonyl)benzyl]piperidine

[0110]. To a solution of sodium hydrogensulfite (4.57 g) and sodium bicarbonate (6.10 g) in water (40 mL) was added 4-[(1-acetyl-4-piperidyl)methyl]benzenesulfonyl chloride (11.46 g) at 75°C under stirring, and the mixture was stirred at 75°C for an hour. Chloroacetic acid (5.14 g) and an aqueous solution of 50% sodium hydroxide (4.4 mL) was added to the reaction solution and stirred for 20 hours under reflux with heat. 1N Hydrochloric acid (20 mL) was added to the reaction mixture at 0°C, and the reaction mixture was extracted with ethyl acetate (60 mL, 30 mL). The organic phase was washed with saturated brine (10 mL×2), dried over magnesium sulfate (anhydrous), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel 150 g, ethyl acetate/methanol=1/0→9/1). The objective fraction was concentrated under reduced pressure to give the title compound as a colorless oil (8.76 g).

¹H NMR (CDCl₃) δ 1.05-1.35 (2H, m), 1.55-1.95 (3H, m), 2.08 (3H, s), 2.4-2.6 (1H, m), 2.66 (2H, d, J=7.4Hz), 2.9-3.1 (1H, m), 3.06 (3H, s), 3.7-3.9 (1H, m), 4.55-4.7 (1H, m), 7.34 (2H, d, J=8.4Hz), 7.87 (2H, d, J=8.4Hz)

20 Reference Example 19-3

4-[4-(Methylsulfonyl)benzyl]piperidine hydrochloride

[0111] A mixture of 1-acetyl-4-[4-(methylsulfonyl)benzyl]-piperidine (8.76 g) and concentrated hydrochloric acid (100 mL) was stirred for 4 hours under reflux with heat. The reaction mixture was concentrated under reduced pressure. 2-Propanol (100 mL) was added thereto and the mixture was concentrated under reduced pressure. To the residue was added 2-propanol (50 mL), and the mixture was stirred under reflux with heat for 30 minutes and cooled down to room temperature. The precipitate was filtered off, washed with 2-propanol (50 mL) and dried under reduced pressure to give the title compound as a white solid (7.51 g).

¹H NMR (CD₃OD) δ 1.3-1.6 (2H, m), 1.75-2.1 (3H, m), 2.75 (2H, d, J=7.0Hz), 2.8-3.05 (2H, m), 3.10 (3H, s), 3.25-3.45 (2H, m), 7.49 (2H, d, J=8.1Hz), 7.89 (2H, d, J=8.1Hz)

35 Reference Example 19-4

4-[4-(Methylsulfonyl)benzyl]piperidine

[0112] 4-[4-(Methylsulfonyl)benzyl]piperidine hydrochloride (1000 mg) was dissolved in water (10 mL). An aqueous solution of 1N sodium hydroxide (5 mL) was added to the solution at 0°C, and the aqueous phase was extracted with dichloromethane (10 mL×3). The organic phase was dried over potassium carbonate and filtered, and the filtrate was concentrated under reduced pressure. Diisopropyl ether (10 mL) was added to the residue, and the precipitate was collected by filtration. The precipitate was washed with diisopropyl ether and dried under reduced pressure to give the title compound as a white solid (712 mg).

¹H NMR (CDCl₃) δ 1.07-1.27 (2H, m), 1.50-1.73 (3H, m), 2.48-2.61 (2H, m), 2.62 (2H, d, J=6.6Hz), 3.03-3.08 (2H, m), 3.05 (3H, s), 7.34 (2H, d, J=8.4Hz), 7.85 (2H, d, J=8.4Hz)

Reference Example 19-5

N-(3-[4-[4-(4-Methylsulfonyl)benzyl]-1-piperidyl]propyl)-aniline dihydrochloride

[0113] Using 4-[4-(methylsulfonyl)benzyl]piperidine, the title compound was synthesized in a manner similar to Reference Example 1. Yield 30%.

¹H NMR (CD₃OD) δ 1.59-2.35 (7H, m), 2.75 (2H, d, J = 6.4 Hz), 2.86-3.05 (2H, m), 3.13 (3H, s), 3.22 (2H, t, J = 7.4 Hz), 3.48 (2H, t, J = 8.0 Hz), 3.59-3.68 (2H, m), 6.63-6.75 (3H, m), 7.10-7.25 (2H, m), 7.50 (2H, d, J = 8.2 Hz), 7.90 (2H, d, J = 8.2 Hz)

Reference Example 20

N-[3-(4-Benzyl-1-piperidiny)propyl]-4-cyanoaniline

[0114] Using 4-cyanoaniline, the title compound was synthesized in a manner similar to Reference Example 1.
¹H NMR (CDCl₃) δ 1.19-1.39 (2H, m), 1.45-1.96 (7H, m), 2.42-2.49 and 2.56-2.60 (2H and 2H, m), 2.90-2.97 and 3.15-3.24 (2H and 2H, m), 6.17-6.30 (1H, br s), 6.45 (2H, d, J=9.0Hz), 7.14-7.42 (7H, m).

Reference Example 21

N-[3-(4-Benzyl-1-piperidiny)propyl]-3-cyanoaniline

[0115] Using 3-cyanoaniline, the title compound was synthesized in a manner similar to Reference Example 1.
¹H NMR (CDCl₃) δ 1.20-1.40 (2H, m), 1.41-1.95 (7H, m), 2.42-2.49 and 2.56-2.60 (2H and 2H, m), 2.91-2.98 and 3.11-3.19 (2H and 2H, m), 6.68-6.74 (2H, m), 6.89-6.93 (1H, m), 7.14-7.30 (6H, m).

Reference Example 22

N-[3-(4-Benzyl-1-piperidiny)propyl]-3-pyridineamine

[0117] Using 3-aminopyridine, the title compound was synthesized in a manner similar to Reference Example 1.
 Yield 38%.

¹H NMR (CDCl₃) δ 1.17-1.93 (9H, m), 2.45 (2H, t, J=6.6Hz), 2.56 (2H, d, J=6.6Hz), 2.93 (2H, m), 3.17 (2H, t, J=6.2Hz), 5.20 (1H, bs), 6.81 (1H, m), 7.03-7.33 (6H, m), 7.91 (1H, dd, J=1.2Hz, 4.8Hz), 7.99 (1H, d, J=2.6Hz).

Reference Example 23-1

tert-Butyl 4-(4-methoxycarbonylbenzyl)piperidine-1-carboxylate

[0118] The mixture of methyl 4-(bromomethyl)benzoate (25 g, 109 mmol and triethyl phosphite (24.3 ml, 142 mmol) was stirred at 150°C for 24 hours. The reaction mixture was distilled under reduced pressure (165-172°C, 1 mmHg) to give diethyl 4-(methylcarbonyl)benzyl phosphonate (21.5 g, 69%).

[0119] Sodium hydride (60% oily, 2.9 g, 71.5 mmol) was added to a solution of diethyl 4-(methylcarbonyl)benzyl phosphonate (20.5 g, 71.5 mmol) and 15-crown 5 (1.4 ml, 7.1 mmol) in THF (120 ml) at 0°C and the mixture was stirred for 0.5 hour at the same temperature. A solution of tert-butyl 4-oxo-1-piperidinecarboxylate (11.9 g, 59.6 mmol) in THF (45 ml) was dropwise added to the mixture at 0°C for 10 minutes, and the mixture was stirred at room temperature for 20 hours. The reaction mixture was poured into an ice-water (200 ml) and the mixture was extracted with ethyl acetate (100 ml×2). The extract was washed with 5% sodium bicarbonate (100 ml) and saturated brine (100 ml) successively, dried over sodium sulfate (anhydrous) and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200 g, ethyl acetate/hexane=1/10) to give tert-butyl 4-(4-methoxycarbonylbenzylidene) piperidine-1-carboxylate (6.9 g, 35%) as a colorless powdery crystal.

[0120] A solution of tert-butyl 4-(4-methoxycarbonylbenzylidene)piperidine-1-carboxylate (6 g, 18 mmol) in methanol (150 ml) was subjected to catalytic hydrogenation in the presence of 10% palladium-carbon (containing 50% water, 1 g) at room temperature for 5 hours. The catalyst was filtered off, and the filtrate was condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel 90 g, ethyl acetate/hexane=1/10) to give the title compound as a pale yellow oil (6.1 g, 100%).

¹H NMR (CDCl₃) δ 1.05-1.42 (2H, m), 1.45 (9H, s), 1.55-1.77 (3H, m), 2.59 (2H, d, J = 7.0Hz), 2.57-2.69 (2H, m), 3.91 (3H, s), 4.04-4.18 (2H, m), 7.21 (2H, d, J = 8.0Hz), 7.96 (2H, d, J = 8.0Hz)

Reference Example 23-2

4-[[1-(tert-Butoxycarbonyl)-4-piperidiny]methyl]benzoic acid

[0121] A mixture of the compound obtained in Reference Example 23-1 (3 g, 9 mmol), ethanol (30 ml) and an aqueous solution of 1N sodium hydroxide (14 ml) was stirred at 80°C for 5 hours. The obtained reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 100 g, ethyl acetate/methanol=10/1) to give the title compound as a white powdery crystal (2.9 g, 99%).

¹H NMR (CDCl₃) δ 1.08-1.26 (2H, m), 1.45 (9H, s), 1.57-1.77 (3H, m), 1.26-2.70 (2H, m), 2.61 (2H, d, J = 7.4Hz), 4.05-4.11 (2H, m), 7.24 (2H, d, J = 8.0Hz), 8.03 (2H, d, J = 8.0Hz)

Reference Example 23-3

tert-Butyl 4-[4-(aminocarbonyl)benzyl]-1-piperidinecarboxylate

- 5 [0122] Hydroxy-1H-benzotriazole (3.6 g, 27 mmol), ammonium chloride (1.9 g, 35.1 mmol), triethylamine (4.9 ml, 35.1 ml) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (6.7 g, 35.1 mmol) were added to a solution of the compound obtained in Reference Example 23-2 (8.6 g, 22.7 mmol) in DMF (160 ml) at 0°C and the mixture was stirred at room temperature for 20 hours. The reaction mixture was concentrated under reduced pressure. Water (200 ml) was added to the residue, and the mixture was extracted with ethyl acetate (200 ml×2). The extract was washed
 10 with 0.5N hydrochloric acid (200 ml), 5% sodium bicarbonate (200 ml) and saturated brine (100 ml) successively, dried over sodium sulfate (anhydrous) and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200 g, ethyl acetate/hexane=1/1→3/1) and recrystallized from hexane to give the title compound as a colorless powdery crystal (8.1 g, 94%).
 15 ¹H NMR (CDCl₃) δ 1.05-1.25 (2H, m), 1.45 (9H, s), 1.56-1.76 (3H, m), 2.59 (2H, d, J = 2.0Hz), 2.57-2.69 (2H, m), 4.04-4.10 (2H, m), 5.50-6.20 (2H, br), 7.22 (2H, d, J = 8.4Hz), 7.74 (2H, d, J = 8.4Hz)

Reference Example 23-4

4-(4-Piperidinylmethyl)benzamide hydrochloride

- 20 [0123] A solution of 4N hydrogen chloride in ethyl acetate (120 ml) was added to a solution of the compound obtained in Reference Example 23-3 (8.1 g, 25.4 mmol) in methanol (120 ml), and the mixture was stirred at room temperature for 3 hours. The obtained solution was concentrated under reduced pressure. The residue was crystallized from diisopropyl ether-ethyl acetate (1/1, 20 ml) to give the title compound as a colorless powdery crystal (5.97 g, 73%).
 25 ¹H NMR (CD₃OD) δ 1.25-1.56 (2H, m), 1.82-2.01 (3H, m), 2.68 (2H, d, J = 6.8Hz), 2.88-3.01 (2H, m), 3.30-3.40 (2H, m), 7.31 (2H, d, J = 8.4Hz), 7.82 (2H, d, J = 8.4Hz)

Reference Example 23-5

30 4-(4-Piperidinylmethyl)benzamide

- [0124] The compound obtained in Reference Example 23-4 (10 g, 39.3 mmol) was added to an aqueous solution of 1N sodium hydroxide (86 ml) at 0°C, and the mixture was stirred at room temperature for an hour. The resulting precipitate was collected by filtration to give the title compound as a colorless powdery crystal (5.96 g, 70%).
 35 ¹H NMR (CDCl₃) δ 1.07-1.30 (2H, m), 1.58-1.75 (4H, m), 2.48-2.60 (4H, m), 3.01-3.07 (2H, m), 5.70-6.40 (2H, br), 7.23 (2H, d, J = 7.4Hz), 7.74 (2H, d, J = 7.4Hz)

Reference Example 23-6

40 4-[[1-(3-Anilinopropyl)-4-piperidinyl]methyl]benzamide hydrochloride

- [0125] Using the compound obtained in Reference Example 23-5 and aniline, the title compound was synthesized in a manner similar to Reference Example 1. Yield 20%.
 45 ¹H NMR (CD₃OD) δ 1.49-1.68 (2H, m), 1.80-2.01 (3H, m), 2.15-2.30 (2H, m), 2.69 (2H, d, J = Hz), 2.89-3.01 (2H, m), 3.17-3.25 (2H, m), 3.46-3.60 (4H, m), 7.31 (2H, d, J = 8.0Hz), 7.43-7.61 (5H, m), 7.82 (2H, d, J = 8.0Hz)

Example 1

50 N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-phenyl-N'-phenylurea hydrochloride

- [0126] To a solution of phenyl isocyanate (163 μl, 1.5 mmol) in THF (15 ml) were added the compound obtained in Reference Example 1 (381 mg, 1.0 mmol) and a solution of triethylamine (308 μl, 2.2 mmol) in dichloromethane (15 ml) at room temperature for an hour under stirring. The mixture was stirred for 12 hours at room temperature. Dichloromethane (50 ml) was added to the mixture, then the mixture was washed with saturated aqueous solution of sodium bicarbonate (50 ml×2). The organic phase was dried over with magnesium sulfate (anhydrous) and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel 12 g, hexane/ethyl acetate=1/1→0/1). The objective fraction was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2 ml), and a solution of 4N hydrogen chloride in ethyl acetate (2 ml) was added thereto. The mixture was

stirred for 5 minutes and concentrated under reduced pressure. Hexane (5 ml) was added to the residue, and the precipitate was collected by filtration and dried under reduced pressure to give the title compound as a white amorphous. Yield 82%.

¹H NMR (DMSO-d₆) δ 1.30-1.95 (7H, m), 2.54-2.57 (2H, m), 2.80-2.93 (2H, m), 3.00-3.12 (2H, m), 3.42-3.80 (2H, m), 3.62-3.78 (2H, m), 6.95-7.55 (15H, m), 7.85 (1H, s)

Anal. Calcd for C₂₈H₃₃N₃O · HCl · 0.75 H₂O: C, 70.42; H, 7.71; N, 8.80. Found: C, 70.43; H, 7.31; N, 8.74.

Example 2

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-phenylurea

[0127] To a solution of the compound obtained in Reference Example 1 (22.9 g, 60 mmol) and triethylamine (18.5 ml, 132 mmol) in dichloromethane (500 ml) was added 4-chlorophenyl isocyanate (13.8 g, 90 mmol) under stirring, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was washed with saturated sodium bicarbonate (400 ml×2), dried over magnesium sulfate (anhydrous) and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel 500 g, hexane/ethyl acetate=1/1→0/1). The objective fraction was concentrated under reduced pressure. The residue was recrystallized from diethyl ether (45 ml). The precipitate was filtered and collected. The precipitate was washed with diethyl ether and dried under reduced pressure to give the title compound as a white crystal (13.8 g, 30 mmol). Yield 50%.

Melting Point 101-103°C

¹H NMR (CDCl₃) δ 1.23-1.46 (2H, m), 1.46-1.90 (7H, m), 2.36 (2H, t, J=7.3Hz), 2.51 (2H, d, J=6.6Hz), 2.82-2.90 (2H, m), 3.77 (2H, t, J=7.3Hz), 6.66 (1H, br), 7.1-7.52 (14H, m)

Anal. Calcd. for C₂₈H₃₂ClN₃O: C, 72.79; H, 6.98; Cl, 7.67; N, 9.09. Found: C, 72.41; H, 6.97; Cl, 7.72; N, 8.98.

Example 3

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(3-chlorophenyl)-N-phenylurea hydrochloride

[0128] Using 3-chlorophenyl isocyanate, the title compound was obtained in a manner similar to Example 1. Yield 72%.

¹H NMR (DMSO-d₆) δ 1.45-1.86 (7H, m), 2.49-2.53 (2H, m), 2.77-2.89 (2H, m), 3.00-3.17 (2H, m), 3.35-3.40 (2H, m), 3.69-3.76 (2H, m), 6.94-6.70 (1H, m), 7.15-7.50 (12H, m), 7.60-7.64 (1H, m), 8.15 (1H, s)

Anal. Calcd for C₂₈H₃₂ClN₃O · HCl · 1.0 H₂O: C, 65.11; H, 6.83; N, 8.14. Found: C, 65.20; H, 6.69; N, 7.95.

Example 4

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-methylphenyl)-N-phenylurea hydrochloride

[0129] Using p-tolyl isocyanate, the title compound was obtained in a manner similar to Example 1. Yield 75%.

¹H NMR (DMSO-d₆) δ 1.45-1.91 (7H, m), 2.21 (3H, s), 2.49-2.53 (2H, m), 2.77-2.85 (2H, m), 3.00-3.18 (2H, m), 3.35-3.44 (2H, m), 3.68-3.76 (2H, m), 6.97-7.02 (2H, m), 7.15-7.50 (12H, m), 7.75 (1H, s)

Anal. Calcd for C₂₉H₃₅N₃O · HCl · 0.75 H₂O: C, 70.85; H, 7.69; N, 8.55. Found: C, 70.85; H, 7.67; N, 8.42.

Example 5

N'-Benzyl-N-[3-(4-benzyl-1-piperidiny)propyl]-N-phenylurea hydrochloride

[0130] Using benzyl isocyanate, the title compound was obtained in a manner similar to Example 1. Yield 67%.

¹H NMR (DMSO-d₆) δ 1.40-1.81 (7H, m), 2.53-2.56 (2H, m), 2.77-2.89 (2H, m), 2.98-3.18 (2H, m), 3.35-3.40 (2H, m), 3.65-3.70 (2H, m), 4.20 (2H, s), 7.18-7.54 (15H, m)

Anal. Calcd. for C₂₉H₃₅N₃O · HCl · 0.5 H₂O: C, 71.51; H, 7.66; N, 8.63. Found: C, 71.60; H, 7.74; N, 8.46.

Example 6

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-cyclohexyl-N-phenylurea

[0131] Using cyclohexyl isocyanate, the title compound was obtained in a manner similar to Example 2. Yield 72%. Melting Point 106-108°C

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¹H NMR (CDCl₃) δ 0.8-1.95 (19H, m), 2.30 (2H, t, J=7.6Hz), 2.50 (2H, d, J=6.6Hz), 2.83 (2H, br d, J=11.8Hz), 3.4-3.75 (1H, m), 3.68 (2H, t, J=7.3Hz), 4.15 (1H, d, J=8.0Hz), 7.05-7.5 (10H, m)
 Anal. Calcd for C₂₈H₃₉N₃O: C, 77.55; H, 9.07; N, 9.69. Found: C, 77.65; H, 8.96; N, 9.75.

5 Example 7

N-[3-(4-Benzyl-1-piperidiny)propyl]-N-phenyl-N'-propylurea

[0132] Using propyl isocyanate, the title compound was obtained in a manner similar to Example 2. Yield 92%.
 10 ¹H NMR (CDCl₃) δ 0.84 (3H, t, J=7.3Hz), 1.1-1.95 (11H, m), 2.33 (2H, t, J=7.6Hz), 2.53 (2H, d, J=6.6Hz), 2.86 (2H, br d, J=11.6Hz), 3.05-3.2 (2H, m), 3.71 (2H, t, J=7.3Hz), 4.55-4.7 (1H, m), 7.1-7.5 (10H, m)

Example 8

15 N-[3-(4-Benzyl-1-piperidiny)propyl]-N-(3-chlorophenyl)-N'-(4-chlorophenyl)urea hydrochloride

[0133] Using the compound obtained in Reference Example 2, the title compound was obtained in a manner similar to Example 2. Yield 27%.
¹H NMR (DMSO-d₆) δ 1.40-1.91 (7H, m), 2.51-2.54 (2H, m), 2.78-2.90 (2H, m), 3.00-3.17 (2H, m), 3.37-3.43 (2H, m),
 20 3.71-3.78 (2H, m), 7.15-7.50 (13H, m), 8.34 (1H, s)
 Anal. Calcd. for C₂₈H₃₁Cl₂N₃O • HCl • 1.0 H₂O: C, 61.04; H, 6.22; N, 7.63. Found: C, 60.80; H, 6.20; N, 7.73.

Example 9

25 N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(3,4-dichlorophenyl)urea

[0134] Using the compound obtained in Reference Example 3, the title compound was obtained in a manner similar to Example 2. Yield 78%.
 Melting Point 128-131°C
 30 ¹H NMR (CDCl₃) δ 1.1-2.0 (9H, m), 2.39 (2H, t, J=6.8Hz), 2.51 (2H, d, J=6.2Hz), 2.88 (2H, br d, J=11.8Hz), 3.78 (2H, t, J=6.6Hz), 7.05-7.4 (10H, m), 7.41 (1H, d, J=2.6Hz), 7.49 (1H, d, J=8.4Hz), 7.90 (1H, br s)

Example 10

35 N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(4-methylphenyl)urea hydrochloride

[0135] Using the compound obtained in Reference Example 4, the title compound was obtained in a manner similar to Example 2. Yield 87%.
¹H NMR (DMSO-d₆) δ 1.2-1.95 (7H, m), 2.34 (3H, s), 2.45-2.6 (2H, m), 2.6-3.5 (6H, m), 3.68 (2H, t, J=6.8Hz), 7.1-7.35 (11H, m), 7.44 (2H, d, J=9.2Hz), 7.93 (1H, s)
 40 Anal. Calcd. for C₂₉H₃₄ClN₃O • HCl • 0.5H₂O: C, 66.79; H, 6.96; Cl, 13.60; N, 8.06. Found: C, 66.84; H, 6.99; Cl, 13.51; N, 7.95.

Example 11

45 N'-(4-Chlorophenyl)-N-[3-[4-(4-fluorobenzyl)-1-piperidiny]propyl]-N-phenylurea

[0136] Using the compound obtained in Reference Example 5, the title compound was obtained in a manner similar to Example 2. Yield 94%.
 50 ¹H NMR (CDCl₃) δ 1.1-2.0 (9H, m), 2.36 (2H, br t, J=7.3Hz), 2.48 (2H, d, J=6.6Hz), 2.86 (2H, br d, J=11.6Hz), 3.77 (2H, t, J=7.1Hz), 6.60 (1H, br s), 6.85-7.55 (13H, m)

Example 12

55 N'-(4-Chlorophenyl)-N-(3,4-dichlorophenyl)-N-[3-[4-(4-fluorobenzyl)-1-piperidiny]propyl]urea

[0137] Using the compound obtained in Reference Example 6, the title compound was obtained in a manner similar to Example 2. Yield 79%.

Melting Point 113-115°C

¹H NMR (CDCl₃) δ 1.1-2.0 (9H, m), 2.40 (2H, br t, J=6.6Hz), 2.48 (2H, d, J=6.6Hz), 2.89 (2H, br d, J=11.4Hz), 3.78 (2H, t, J=6.8Hz), 6.9-7.4 (9H, m), 7.42 (1H, d, J=2.6Hz), 7.50 (1H, d, J=8.8Hz), 7.77 (1H, br s)

5 Example 13

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-(1-naphthyl)-N-phenylurea

[0138] Using 1-naphthyl isocyanate, the title compound was obtained in a manner similar to Example 2. Yield 74%.

10 Melting Point 124-127°C

¹H NMR (CDCl₃) δ 1.0-1.95 (9H, m), 2.3-2.5 (2H, m), 2.39 (2H, d, J=6.6Hz), 2.86 (2H, br d, J=11.4Hz), 3.88 (2H, t, J=7.3Hz), 7.0-7.3 (6H, m), 7.3-7.65 (10H, m), 7.75-7.85 (1H, m), 7.9-8.0 (1H, m)

Anal. Calcd for C₃₂H₃₅N₃O: C, 80.47; H, 7.39; N, 8.80. Found: C, 80.33; H, 7.21; N, 8.83.

15 Example 14

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(2,6-dimethylphenyl)urea trifluoroacetate

[0139] Triethylamine (14 µl, 100 µmol) was added to a solution of the compound obtained in Reference Example 7 (16.1 mg, 50 µmol) in dichloromethane (0.3 ml) at room temperature. Then, a solution of 2,6-dimethylphenyl isocyanate (11.0 mg, 75 µmol) in dichloromethane (0.4 ml) was added thereto at room temperature, and the mixture was stirred for 24 hours. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was dissolved again in dichloromethane (0.5 ml). PS-trisamine resin (Argonaut, 3.62 mmol/g, 50 mg, 0.18 mmol) was added to the solution and the solution was stirred at room temperature for an hour. The resin was separated by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved again in dichloromethane (0.5 ml). MP-carbonate resin (Argonaut, 2.64 mmol/g, 45 mg, 0.12 mmol) was added to the solution and stirred at room temperature for an hour. The resin was filtered off, and the filtrate was concentrated under reduced pressure and purified by preparative HPLC. The objective fraction was concentrated to give the title compound as a colorless oil (15.1 mg).

30 HPLC analysis (220 nm): purity 96% (Retention time 3.448 min) MS (APCI⁺) 470 (M+1)

Example 15

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(2-chlorophenyl)urea trifluoroacetate

35 [0140] Using 2-chlorophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 98% (Retention time 3.537 min) MS (APCI⁺) 476 (M+1)

Example 16

40 N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(4-fluorophenyl)urea trifluoroacetate

[0141] Using 4-chlorophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 98% (Retention time 3.464 min) MS (APCI⁺) 460(M+1)

45

Example 17

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(4-methylthiophenyl)urea trifluoroacetate

50 [0142] Using 4-methylthiophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 96% (Retention time 3.587 min) MS (APCI⁺) 488 (M+1)

Example 18

55 N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(1-naphthyl)urea trifluoroacetate

[0143] Using 1-naphthyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 93% (Retention time 3.570 min) MS (APCI⁺) 492 (M+1)

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Example 19

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(3-methylphenyl)urea trifluoroacetate

- 5 [0144] Using 3-methylphenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 94% (Retention time 3.549 min) MS (APCI⁺) 456 (M+1)

Example 20

- 10 N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(2,6-difluorophenyl)urea trifluoroacetate

[0145] Using 2,6-difluorophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 99% (Retention time 3.361 min) MS (APCI⁺) 478 (M+1)

Example 21

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(2,4-dimethoxyphenyl)urea trifluoroacetate

- 20 [0146] Using 2,4-dimethoxyphenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 97% (Retention time 3.482 min) MS (APCI⁺) 502 (M+1)

Example 22

- 25 N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(2-(trifluoromethyl)phenyl)urea trifluoroacetate

[0147] Using 2-(trifluoromethyl)phenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 98% (Retention time 3.760 min) MS (APCI⁺) 510 (M+1)

Example 23

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(4-chlorophenyl)urea trifluoroacetate

- 35 [0148] Using 4-chlorophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 93% (Retention time 3.551 min) MS (APCI⁺) 476 (M+1)

Example 24

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(3,4-dichlorophenyl)urea trifluoroacetate

- 40 [0149] Using 3,4-dichlorophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 96% (Retention time 3.613 min) MS (APCI⁺) 510 (M+1)

Example 25

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(4-isopropylphenyl)urea trifluoroacetate

- 50 [0150] Using 4-isopropylphenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 95% (Retention time 3.764 min) MS (APCI⁺) 484 (M+1)

Example 26

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(4-nitrophenyl)urea trifluoroacetate

- 55 [0151] Using 4-nitrophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 92% (Retention time 3.775 min) MS (APCI⁺) 487 (M+1)

Example 27

N-Benzyl-N-[3-(4-benzyl-1-piperidiny)propyl]-N'-(4-bromophenyl)urea trifluoroacetate

- 5 [0152] Using 4-bromophenyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 93% (Retention time 3.485 min) MS (APCI⁺) 520 (M+1)

Example 28

- 10 N-Benzyl-N-[3-(4-benzyl-1-piperidiny)propyl]-N'-(4-methoxyphenyl)urea trifluoroacetate

[0153] Using 4-methoxyphenyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 97% (Retention time 3.405 min) MS (APCI⁺) 472 (M+1)

Example 29

N-Benzyl-N-[3-(4-benzyl-1-piperidiny)propyl]-N'-[2-(trifluoromethoxy)phenyl]urea trifluoroacetate

- 20 [0154] Using 2-(trifluoromethoxy)phenyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 100% (Retention time 3.637 min) MS (APCI⁺) 526 (M+1)

Example 30

- 25 N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(4-fluorobenzyl)urea trifluoroacetate

[0155] Triethylamine (14 μ l, 100 μ mol) was added to a solution of the compound obtained in Reference Example 8 (16.1 mg, 50 μ mol) in dichloromethane (0.3 ml) at room temperature. Then, a solution of 4-chlorophenyl isocyanate (11.5 mg, 75 μ mol) in dichloromethane (0.4 ml) was added to the solution at room temperature and the mixture was stirred for 24 hours. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was dissolved again in dichloromethane (0.5 ml). PS-Tris amine resin (Argonaut, 3.62 mmol/g, 50 mg, 0.18 mmol) was added to the solution and the mixture was stirred at room temperature for an hour. The resin was filtered off, and the filtrate was concentrated under reduced pressure and dissolved again in dichloromethane (0.5 ml). MP-carbonate resin (Argonaut, 2.64 mmol/g, 45 mg, 0.12 mmol) was added to the solution and the mixture was stirred at room temperature for an hour. The resin was filtered off, and the filtrate was concentrated under reduced pressure and purified by preparative HPLC. The objective fraction was concentrated to give the title compound as a colorless oil (13.9 mg).
HPLC analysis (220 nm): purity 99% (Retention time 3.564 min) MS (APCI⁺) 494 (M+1)

Example 31

N-[3-(4-Benzyl-1-piperidiny)propyl]-N-(3-chlorobenzyl)-N'-(4-chlorophenyl)urea trifluoroacetate

- 45 [0156] Using the compound obtained in Reference Example 9, the title compound was synthesized in a manner similar to Example 30.
HPLC analysis (220 nm): purity 94% (Retention time 3.582 min) MS (APCI⁺) 510 (M+1)

Example 32

- 50 N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(3,4-dichlorobenzyl)urea trifluoroacetate

[0157] Using the compound obtained in Reference Example 10, the title compound was synthesized in a manner similar to Example 30.
HPLC analysis (220 nm): purity 93% (Retention time 3.637 min) MS (APCI⁺) 544 (M+1)

55

Example 33

N-[3-(4-Benzyl-1-piperidiny)propyl]-N-(4-fluorobenzyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

- 5 [0158] Triethylamine (14 μ l, 100 μ mol) was added to a solution of the compound obtained in Reference Example 8 (16.1 mg, 50 μ mol) in dichloromethane (0.3 ml) at room temperature. Then, a solution of 4-methoxyphenyl isocyanate (11.2 mg, 75 μ mol) in dichloromethane (0.4 ml) was added to the solution at room temperature and the mixture was stirred for 24 hours. After the reaction was completed, the reaction solution was concentrated under reduced pressure and dissolved again in dichloromethane (0.5 ml). PS-TRIS amine resin (Argonaut, 3.62 mmol/g, 50 mg, 0.18 mmol) was added to the solution and stirred at room temperature for an hour. The resin was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved again in dichloromethane (0.5 ml). MP-carbonate resin (Argonaut, 2.64 mmol/g, 45 mg, 0.12 mmol) was added to the solution and stirred at room temperature for an hour. The resin was filtered off, and the filtrate was concentrated under reduced pressure and purified by preparative HPLC. The objective fraction was concentrated to give the title compound as a colorless oil (12.6 mg).
- 10 HPLC analysis (220 nm): purity 96% (Retention time 3.471 min) MS (APCI⁺) 490 (M+1)

Example 34

20 N-[3-(4-Benzyl-1-piperidiny)propyl]-N-(3-chlorobenzyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

- [0159] Using the compound obtained in Reference Example 9, the title compound was synthesized in a manner similar to Example 33.
- HPLC analysis (220 nm): purity 99% (Retention time 3.483 min) MS (APCI⁺) 506 (M+1)

Example 35

N-[3-(4-Benzyl-1-piperidiny)propyl]-N-(3,4-dichlorobenzyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

- 30 [0160] Using the compound obtained in Reference Example 10, the title compound was synthesized in a manner similar to Example 33.
- HPLC analysis (220 nm): purity 97% (Retention time 3.521 min) MS (APCI⁺) 540 (M+1)

Example 36

35 N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-cyclohexyl-N-(4-fluorobenzyl)urea trifluoroacetate

- [0161] Triethylamine (14 μ l, 100 μ mol) was added to a solution of the compound obtained in Reference Example 8 (16.1 mg, 50 μ mol) in dichloromethane (0.3 ml) at room temperature. Then, a solution of cyclohexyl isocyanate (9.4 mg, 75 μ mol) in dichloromethane (0.4 ml) was added to the mixture at room temperature, and the mixture was stirred for 24 hours. After the reaction was completed, the reaction mixture was concentrated under reduced pressure and dissolved again in dichloromethane (0.5 ml). PS-TRIS amine resin (Argonaut, 3.62 mmol/g, 50 mg, 0.18 mmol) was added to the solution and stirred at room temperature for an hour. The resin was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved again in dichloromethane (0.5 ml). MP-carbonate resin (Argonaut, 2.64 mmol/g, 45 mg, 0.12 mmol) was added to the solution and stirred at room temperature for an hour. The resin was filtered off, and the filtrate was concentrated under reduced pressure and purified by preparative HPLC. The objective fraction was concentrated to give the title compound as a colorless oil (12.2 mg).
- 40 HPLC analysis (220 nm): purity 100% (Retention time 3.500 min) MS (APCI⁺) 466 (M+1)

Example 37

50 N-[3-(4-Benzyl-1-piperidiny)propyl]-N-(3-chlorobenzyl)-N'-cyclohexylurea trifluoroacetate

- [0162] Using the compound obtained in Reference Example 9, the title compound was synthesized in a manner similar to Example 36.
- 55 HPLC analysis (220 nm): purity 100% (Retention time 3.579 min) MS (APCI⁺) 482 (M+1)

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Example 38

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-cyclohexyl-N-(3,4-dichlorobenzyl)urea trifluoroacetate

5 [0163] Using the compound obtained in Reference Example 10, the title compound was synthesized in a manner similar to Example 36.

HPLC analysis (220 nm): purity 99% (Retention time 3.753 min) MS (APCI⁺) 516 (M+1)

Example 39

10

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-(4-chlorophenyl)-N-(2,6-difluorobenzyl)urea trifluoroacetate

[0164] Using the compound obtained in Reference Example 11, the title compound was synthesized in a manner similar to Example 30.

15 HPLC analysis (220 nm): purity 98% (Retention time 3.623 min) MS (APCI⁺) 512 (M+1)

Example 40

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(2-chlorobenzyl)-N'-(4-chlorophenyl)urea trifluoroacetate

20

[0165] Using the compound obtained in Reference Example 12, the title compound was synthesized in a manner similar to Example 30.

HPLC analysis (220 nm): purity 100% (Retention time 3.588 min) MS (APCI⁺) 510 (M+1)

Example 41

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(4-chlorobenzyl)-N'-(4-chlorophenyl)urea trifluoroacetate

25

[0166] Using the compound obtained in Reference Example 13, the title compound was synthesized in a manner similar to Example 30.

30

HPLC analysis (220 nm): purity 99% (Retention time 3.595 min) MS (APCI⁺) 510 (M+1)

Example 42

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-(4-chlorophenyl)-N-(4-methylbenzyl)urea trifluoroacetate

35

[0167] Using the compound obtained in Reference Example 14, the title compound was synthesized in a manner similar to Example 30.

HPLC analysis (220 nm): purity 91% (Retention time 3.841 min) MS (APCI⁺) 490 (M+1)

40

Example 43

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-(4-chlorophenyl)-N-(4-methoxybenzyl)urea trifluoroacetate

45

[0168] Using the compound obtained in Reference Example 15, the title compound was synthesized in a manner similar to Example 30.

HPLC analysis (220 nm): purity 95% (Retention time 3.521 min) MS (APCI⁺) 506 (M+1)

Example 44

50

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(2,6-difluorobenzyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

[0169] Using the compound obtained in Reference Example 11, the title compound was synthesized in a manner similar to Example 33.

55

HPLC analysis (220 nm): purity 99% (Retention time 3.511 min) MS (APCI⁺) 508 (M+1)

Example 45

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(2-chlorobenzyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

- 5 [0170] Using the compound obtained in Reference Example 12, the title compound was synthesized in a manner similar to Example 33.
HPLC analysis (220 nm): purity 99% (Retention time 3.469 min) MS (APCI⁺) 506 (M+1)

Example 46

10 N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(4-chlorobenzyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

- [0171] Using the compound obtained in Reference Example 13, the title compound was synthesized in a manner similar to Example 33.
15 HPLC analysis (220 nm): purity 99% (Retention time 3.475 min) MS (APCI⁺) 506 (M+1)

Example 47

20 N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-(4-methoxyphenyl)-N-(4-methylbenzyl)urea trifluoroacetate

- [0172] Using the compound obtained in Reference Example 14, the title compound was synthesized in a manner similar to Example 33.
HPLC analysis (220 nm): purity 94% (Retention time 3.719 min) MS (APCI⁺) 486 (M+1)

Example 48

25 N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(4-methoxybenzyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

- [0173] Using the compound obtained in Reference Example 15, the title compound was synthesized in a manner similar to Example 33.
30 HPLC analysis (220 nm): purity 97% (Retention time 3.403 min) MS (APCI⁺) 502 (M+1)

Example 49

35 N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-cyclohexyl-N-(2,6-difluorobenzyl)urea trifluoroacetate

- [0174] Using the compound obtained in Reference Example 11, the title compound was synthesized in a manner similar to Example 36.
40 HPLC analysis (220 nm): purity 88% (Retention time 3.549 min) MS (APCI⁺) 484 (M+1)

Example 50

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(2-chlorobenzyl)-N'-cyclohexylurea trifluoroacetate

- 45 [0175] Using the compound obtained in Reference Example 12, the title compound was synthesized in a manner similar to Example 36.
HPLC analysis (220 nm): purity 98% (Retention time 3.521 min) MS (APCI⁺) 482 (M+1)

Example 51

50 N-[3-(4-Benzyl-1-piperidinyl)propyl]-N-(4-chlorobenzyl)-N'-cyclohexylurea trifluoroacetate

- [0176] Using the compound obtained in Reference Example 13, the title compound was synthesized in a manner similar to Example 36.
55 HPLC analysis (220 nm): purity 99% (Retention time 3.515 min) MS (APCI⁺) 482 (M+1)

Example 52

N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-cyclohexyl-N-(4-methylbenzyl)urea trifluoroacetate

- 5 [0177] Using the compound obtained in Reference Example 14, the title compound was synthesized in a manner similar to Example 36.
HPLC analysis (220 nm): purity 94% (Retention time 3.776 min) MS (APCI⁺) 462 (M+1)

Example 53

10 N-[3-(4-Benzyl-1-piperidinyl)propyl]-N'-cyclohexyl-N-(4-methoxybenzyl)urea trifluoroacetate

- [0178] Using the compound obtained in Reference Example 15, the title compound was synthesized in a manner similar to Example 36.
15 HPLC analysis (220 nm) : purity 100% (Retention time 3.448 min) MS (APCI⁺) 478 (M+1)

Example 54

20 Ethyl {N'-Benzyl-N'-[3-(4-benzyl-1-piperidinyl)propyl]ureido}-acetate trifluoroacetate

- [0179] Using ethyl isocyanatoacetate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 97% (Retention time 2.883 min) MS (APCI⁺) 452 (M+1)

Example 55

25 N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-tert-butylurea trifluoroacetate

- [0180] Using tert-butylisocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 99% (Retention time 3.531 min) MS (APCI⁺) 422 (M+1)

Example 56

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-[(1S)-1-(1-naphthyl)ethyl]urea trifluoroacetate

- 35 [0181] Using (1S)-1-(1-naphthyl)ethyl isocyanate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 100% (Retention time 3.800 min)
MS (APCI⁺) 520 (M+1)

Example 57

40 N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-hexylurea trifluoroacetate

- [0182] Using hexyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 99% (Retention time 3.732 min) MS (APCI⁺) 450 (M+1)

Example 58

N-Benzyl-N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-cyclohexylurea trifluoroacetate

- 50 [0183] Using cyclohexyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 99% (Retention time 3.598 min) MS (APCI⁺) 448 (M+1)

Example 59

55 Diethyl (2S)-2-{N'-benzyl-N'-[3-(4-benzyl-1-piperidinyl)propyl]ureido}glutarate trifluoroacetate

- [0184] Using diethyl (2S)-2-isocyanatoglutarate, the title compound was synthesized in a manner similar to Example 14. HPLC analysis (220 nm): purity 100% (Retention time 3.501 min)

MS (APCI⁺) 552 (M+1)

Example 60

5 N,N'-Dibenzyl-N-[3-(4-benzyl-1-piperidiny)propyl]urea trifluoroacetate

[0185] Using benzyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 100% (Retention time 3.491 min) MS (APCI⁺) 456 (M+1)

10 **Example 61**

Methyl (2S)-2-{N'-benzyl-N'-[3-(4-benzyl-1-piperidiny)propyl]-ureido}-4-methylpentanoate trifluoroacetate

15 [0186] Using methyl (2S)-2-isocyanato-4-methylpentanoate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 99% (Retention time 3.587 min) MS (APCI⁺) 494 (M+1)

Example 62

20 N'-(1-Adamantyl)-N-benzyl-N-[3-(4-benzyl-1-piperidiny)propyl]urea trifluoroacetate

[0187] Using 1-adamantyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 99% (Retention time 3.969 min)
MS (APCI⁺) 500 (M+1)

25

Example 63

N-Benzyl-N-[3-(4-benzyl-1-piperidiny)propyl]-N'-(3-isopropenyl- α,α -dimethylbenzyl)urea trifluoroacetate

30 [0188] Using 3-isopropenyl- α,α -dimethylbenzyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 99% (Retention time 3.987 min) MS (APCI⁺) 524 (M+1)

Example 64

35

N-Benzyl-N-[3-(4-benzyl-1-piperidiny)propyl]-N'-propylurea trifluoroacetate

[0189] Using propyl isocyanate, the title compound was synthesized in a manner similar to Example 14.
HPLC analysis (220 nm): purity 99% (Retention time 3.318 min) MS (APCI⁺) 408 (M+1)

40

Example 65

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(cyclohexylmethyl)urea trifluoroacetate

45 [0190] Using the compound obtained in Reference Example 16, the title compound was synthesized in a manner similar to Example 30.
HPLC analysis (220 nm): purity 97% (Retention time 3.917 min) MS (APCI⁺) 482 (M+1)

Example 66

50

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(3-pyridylmethyl)urea trifluoroacetate

[0191] Using the compound obtained in Reference Example 17, the title compound was synthesized in a manner similar to Example 30.
55 HPLC analysis (220 nm): purity 98% (Retention time 2.879 min)
MS (APCI⁺) 477 (M+1)

Example 67

N-{3-(4-Benzyl-1-piperidiny)propyl}-N'-(cyclohexylmethyl)-N'-(4-methoxyphenyl)urea trifluoroacetate

5 [0192] Using the compound obtained in Reference Example 16, the title compound was synthesized in a manner similar to Example 33.

HPLC analysis (220 nm): purity 94% (Retention time 2.946 min) MS (APCI⁺) 478 (M+1)

Example 68

10

N-{3-(4-Benzyl-1-piperidiny)propyl}-N'-(4-methoxyphenyl)-N-(3-pyridylmethyl)urea trifluoroacetate

[0193] Using the compound obtained in Reference Example 17, the title compound was synthesized in a manner similar to Example 33.

15 HPLC analysis (220 nm): purity 97% (Retention time 1.917 min)

MS (APCI⁺) 473 (M+1)

Example 69

20 N-{3-(4-Benzyl-1-piperidiny)propyl}-N'-cyclohexyl-N-(cyclohexylmethyl)urea trifluoroacetate

[0194] Using the compound obtained in Reference Example 16, the title compound was synthesized in a manner similar to Example 36.

HPLC analysis (220 nm): purity 100% (Retention time 3.842 min)

25 MS (APCI⁺) 454 (M+1)

Example 70

30 N-{3-(4-Benzyl-1-piperidiny)propyl}-N'-cyclohexyl-N-(3-pyridylmethyl)urea trifluoroacetate

[0195] Using the compound obtained in Reference Example 17, the title compound was synthesized in a manner similar to Example 36.

HPLC analysis (220 nm): purity 99% (Retention time 2.801 min)

35 MS (APCI⁺) 449 (M+1)

Example 71

N'-(4-Chlorophenyl)-N-(3-{4-[4-(4-morpholynylsulfonyl)benzyl]-1-piperidiny)propyl)-N-phenylurea hydrochloride

40 [0196] Using the compound obtained in Reference Example 18-4, the title compound was synthesized in a manner similar to Example 2. Yield 54%.

¹H NMR (CD₃OD) δ 1.09-1.27 (1H, m), 1.49 - 1.74 (2H, m), 1.81 - 2.06 (4H, m), 2.75 (2H, d, J = 6.6 Hz), 2.94 (4H, t, J = 4.6 Hz), 3.19 (2H, t, J = 6.4 Hz), 3.29 - 3.32 (2H, m), 3.55 - 3.62 (2H, m), 3.70 (4H, t, J = 4.6 Hz), 3.86 (2H, t, J = 6.4 Hz), 7.20 - 7.33 (5H, m), 7.40 - 7.58 (7H, m), 7.71 (2H, d, J = 8.0 Hz)

45

Example 72

N'-(4-Chlorophenyl)-N-(3-{4-[4-(4-methylsulfonyl)benzyl]-1-piperidiny)propyl)-N-phenylurea hydrochloride

50 [0197] Using the compound obtained in Reference Example 19-5, the title compound was synthesized in a manner similar to Example 2. Yield 57%.

Free base: ¹H NMR (CDCl₃) δ 1.23 - 2.18 (9H, m), 2.39 - 2.54 (2H, m), 2.62 (2H, d, J = 5.6 Hz), 2.88 - 3.03 (2H, m), 3.05 (3H, s), 3.77 (2H, t, J = 7.4 Hz), 6.43 (1H, s), 7.16 - 7.53 (11H, m), 7.85 (2H, d, J = 8.4 Hz)

55

Example 73

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(4-cyanophenyl)urea

- 5 **[0198]** Using the compound obtained in Reference Example 20, the title compound was synthesized in a manner similar to Example 2. Yield 67%.
¹H NMR (CDCl₃) δ 1.20-1.40 (2H, m), 1.48-2.04 (7H, m), 2.28-2.60 (4H, m), 2.86-2.99 (2H, m), 3.91 (2H, t, J=6.2Hz), 7.05-7.45 (11H, m), 7.68 (2H, d, J=8.8Hz), 8.90 (1H, brs).

10 **Example 74**

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(3-cyanophenyl)urea hydrochloride

- 15 **[0199]** Using the compound obtained in Reference Example 21, the title compound was synthesized in a manner similar to Example 2. Yield 57%.
 Free base: ¹H NMR (CDCl₃) δ 1.20-1.40 (2H, m), 1.45-1.81 (5H, m), 1.85-2.02 (2H, m), 2.04 (3H, s), 2.38-2.57 (4H, m), 2.85-2.98 (2H, m), 3.83 (2H, t, J=6.4Hz), 7.07-7.40 (11H, m), 7.44-7.60 (2H, m), 8.53 (1H, brs).

20 **Example 75**

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-(3-pyridiny)urea hydrochloride

- 25 **[0200]** 4-Chlorophenyl isocyanate (297 mg) was added to a solution of N-[3-(4-benzyl-1-piperidiny)propyl]-3-pyridineamine (400 mg) in tetrahydrofuran (5 ml) and the mixture was stirred for 15 hours. Ethyl acetate (15 ml) and saturated sodium bicarbonate (15 ml) were added to the reaction mixture. The organic phase was separated, washed with water (10 ml) and saturated brine (10 ml) and dried over sodium sulfate (anhydrous), and the solvent was removed. The residue was purified by silica gel column chromatography (20 g). The fraction eluted by ethyl acetate-methanol (10:1) was collected and concentrated under reduced pressure. A solution of 4N hydrogen chloride in ethyl acetate (1.0 ml) was added to the residue. The precipitate was filtered and collected, and dried under reduced pressure to give the title compound (555 mg, Yield 76.0%).
 Free base: ¹H NMR (CDCl₃) δ 1.43-1.86 (9H, m), 2.43 (2H, t, J=6.6Hz), 2.51 (2H, d, J=6.2Hz), 2.90 (3H, m), 3.82 (2H, t, J=6.6Hz), 7.09-7.40 (10H, m), 7.64 (1H, m), 8.01 (1H, bs), 8.52-8.58 (2H, m).

35 **Example 76**

N-[3-(4-Benzyl-1-piperidiny)propyl]-N'-(4-chlorophenyl)-N-phenylurea hydrochloride

- 40 **[0201]** Using 4-chlorophenyl isocyanate, the title compound was synthesized in a manner similar to Example 1. Yield 60%.
¹H NMR (DMSO-d₆) δ 1.3-2.0 (7H, m), 2.45-2.6 (2H, m), 2.6-3.5 (6H, m), 3.65-3.8 (2H, m), 7.1-7.55 (14H, m), 8.08 (1H, s)

45 **Example 77**

4-[[1-(3-[[[(4-Chloroanilino)carbonyl]anilino]propyl]-4-piperidiny)methyl]benzamide

- 50 **[0202]** Using the compound obtained in Reference Example 23-6, the title compound was synthesized in a manner similar to Example 2. Yield 58%.
¹H NMR (CDCl₃) δ 1.17-1.39 (2H, m), 1.40-1.90 (7H, m), 2.32-2.39 (2H, m), 2.56 (2H, d, J = 5.8Hz), 2.83-2.88 (2H, m), 3.73-3.80 (2H, m), 5.40-6.20 (2H, br), 6.58 (1H, brs), 7.16-7.51 (11H, m), 7.14 (2H, d, J = 8.6Hz)

Test Example

- 55 (1) Cloning of human CCR5 chemokine receptor

[0203] Cloning of CCR5 gene was carried out by PCR (polymerase chain reaction) from human spleen cDNA. With using 0.5 ng of spleen cDNA (Toyobo, QUICK-Clone cDNA) as a template, PCR was performed in DNA Thermal Cycler

480 (Perkin-Elmer) (reaction conditions: 30 cycles of 95°C for 1 minute, 60°C for 1 minute, and 75°C for 5 minutes) by adding primer set,

5 5' - CAGGATCCGATGGATTATCAAGTGTCAAGTCCAA -3' (25 pmol)

and

10 5' - TCTAGATCACAAAGCCCACAGATATTTCTGCTCC -3' (25 pmol),

which were designed referring to nucleotide sequence of CCR5 gene reported by Samson et al. (Biochemistry, 35(11), 3362-3367 (1996)) and by using TaKaRa EX Taq (Takara Shuzo). The resultant PCR product was subjected to agarose gel electrophoresis to collect about 1.0kb DNA fragment, which was subjected to Original TA Cloning Kit (Funakoshi) to carry out cloning of CCR5 gene.

(2) Preparation of plasmid for expression of human CCR5

[0204] The plasmid obtained in the above (1) was digested with restriction enzymes XbaI (Takara Shuzo) and BamHI (Takara Shuzo) and subjected to agarose gel electrophoresis to collect about 1.0kb DNA fragment. The DNA fragment was mixed with plasmid pcDNA3.1 (Funakoshi) for expression in animal cells, said plasmid being digested with XbaI and BamHI, and they were ligated with DNA Ligation Kit Ver.2 (Takara Shuzo). The resulting plasmid was subjected to transformation of competent cell of E. coli JM109 (Takara Shuzo) to give plasmid pCCR5.

25 (3) Introduction of plasmid for expression of human CCR5 into CHO-K1 cell and Expression of the plasmid in CHO-K1 cell

[0205] CHO-K1 cells were grown in 750 ml of tissue culture flask (Becton Dickinson) using Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum (Life Tech Oriental) and took off with 0.5 g/L trypsin-0.2 g/L EDTA (Life Tech Oriental). The cells were washed with PBS (Life Tech Oriental), centrifuged (1000 rpm, 5 minutes), and suspended in PBS. With using Gene Pulser (Bio-Rad Laboratories), DNA was introduced into the cells under the conditions shown below. That is, to the cuvette having 0.4 cm gap were added 8×10^6 cells and 10 µg of plasmid pCCR5 for expression of human CCR5, and electroporation was carried out under 0.25 kV of voltage and 960 µF of capacitance. The cells were transferred into Ham's F12 medium containing 10% fetal calf serum, and cultivated for 24 hours. The cells were again took off and centrifuged, and suspended in Ham's F12 medium containing 10% fetal calf serum and 500 µg/ml of geneticin (Life Tech Oriental). The suspension was diluted to give 10^4 cells/ml of the suspension, which was inoculated on 96 well plate (Becton Dickinson) to give geneticin resistant cells.

[0206] Then, the resulting geneticin resistant cells were cultivated in 96 well plate (Becton Dickinson), and cells expressing CCR5 were selected from the geneticin resistant cells. That is, in an assay buffer (Ham's F12 medium containing 0.5% BSA and 20 mM HEPES (Wako Pure Chemical, pH 7.2) to which was added 200 pM of [125 I]-RANTES (Amersham) as a ligand, binding reaction was carried out at room temperature for 40 minutes, and the buffer was washed with ice-cooled PBS. To the buffer was added 50 µl/well of 1M NaOH, and the mixture was stirred. Radioactivity was determined with γ-counter to select CHO/CCR5 cells which specifically bound with the ligand.

45 (4) Evaluation of Test Compounds based on CCR5 antagonistic activity

[0207] The CHO/CCR5 were inoculated on 96 well microplate (5×10^4 cells/well) and cultivated for 24 hours. The medium was removed by means of suction, and to each well was added assay buffer containing Test Compound (1 µl) and then 100 pM of [125 I]-RANTES (Amersham) as a ligand. The reaction was carried out at room temperature for 40 minutes, and assay buffer was removed by means of suction. Each well was washed twice with cooled PBS, and 200 µl of Microscinti-20 (Packard Instrument, Inc.) was added to each well. Radioactivity was determined with Top-Count Micro Scintillation Counter (Packard Instrument, Inc.).

[0208] According to the method described above, the inhibition rate of the test compounds for CCR5 binding was determined.

55 [0209] The results are shown in Table 1.

EP 1 219 605 A1

Example Number	Inhibition Rate (%) at 1.0 μ M
1	96
7	92
10	100
12	92
13	67
71	98
72	94

(5) Inhibitory effect on HIV-1 infection to MAGI-CCR5 cell

[0210] The plasmid where β -galactosidase gene was ligated to the downstream of HIV-1 LTR was introduced into CD4 positive HeLa cell, to which human CCR5 was further introduced to obtain transformant MAGI-CCR5. By using said transformant MAGI-CCR5, the degree of HIV-1 infection was calculated from β -galactosidase activity (blue color due to decomposition of 5-bromo-4-chloro-3-indolyl- β -D-galactopyranoside). Specifically, MAGI-CCR5 cells were suspended in DMEM medium containing 10% serum to prepare 5×10^4 cells/ml suspension. To each well of 96 well plate was inoculated 200 μ l of the suspension, and the cells were cultivated at 37°C overnight. The medium was removed by means of suction, and to the residue was added 100 μ l of the above medium containing 0.32 μ M of Test Compound and 100 μ l of the above medium containing 300PFU of HIV-1 Ba-L cells. The final concentration of the test compound was 0.16 μ M. The cells were cultivated at 37°C for 2 days. The medium was removed by means of suction. To the residue was added 200 μ l of cell fixative (PBS containing 1% formaldehyde and 0.2% glutaraldehyde), and the mixture was allowed to stand at room temperature for 5 minutes and washed twice with PBS. To the mixture was added 100 μ l of staining solution (PBS containing 4 μ M potassium ferrocyanide, 4 μ M potassium ferricyanide, 2 μ M $MgCl_2$ and 0.4 mg/ml X-gal), and the mixture was allowed to stand at 37°C for 50 minutes and washed twice with PBS. The number of blue cells was counted by microscope and defined as the number of cells infected with HIV-1. According to this method, inhibition rate on HIV-1 infection was determined and found that Compounds obtained from Example 76 shows 98% inhibition on HIV-1 infection.

[0211] The pharmaceutical composition for antagonizing CCR5 (e.g. a medicament for the treatment or prevention of infectious disease of HIV, a medicament for the treatment or prevention of AIDS, etc.) comprising the compound (I) of the present invention, as an active ingredient, can be prepared, for example, by the following prescriptions:

Preparations

1. Capsule

[0212]

(1) Compound obtained in Working Example 1	40 mg
(2) Lactose	70 mg
(3) Fine crystalline cellulose	9 mg
(4) Magnesium stearate	1 mg
1 capsule 120 mg	

[0213] (1), (2), (3) and 1/2 of (4) are mixed and then granulated. To the granules is added the remainder of (4), and the whole is filled into a gelatin capsule.

2. Tablet

[0214]

(1) Compound obtained in Working Example 10	40 mg
(2) Lactose	58 mg

(continued)

(3) Corn starch	18 mg
(4) Fine crystalline cellulose	3.5 mg
(5) Magnesium stearate	0.5 mg
1 tablet 120 mg	

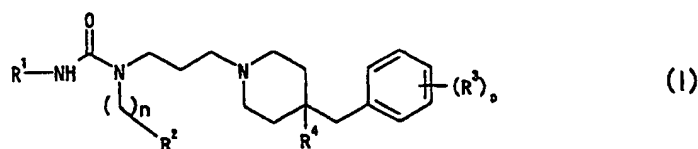
[0215] (1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the mixture to compression molding.

INDUSTRIAL APPLICABILITY

[0216] The compound of the formula (I) or salt thereof of the present invention has superior CCR5 antagonistic activity and can be advantageously used for the treatment or prevention of various infectious disease of HIV in human (e.g. AIDS).

Claims

1. A compound of the formula:



[wherein

R^1 is a hydrocarbon group which may be substituted;

R^2 is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;

R^3 is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C_{1-4} alkyl group which may be substituted, a C_{1-4} alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;

R^4 is a hydrogen atom or a hydroxy group;

n is an integer of 0 or 1;

p is an integer of 0 or 1 to 4]; or a salt thereof.

2. The compound as claimed in claim 1, wherein R^3 is a halogen atom, a C_{1-4} alkyl group which may be substituted, a C_{1-4} alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group.

3. The compound as claimed in claim 1, wherein R^1 is an alicyclic hydrocarbon group which may be substituted or an aryl group which may be substituted.

4. The compound as claimed in claim 1, wherein R^1 is a hydrocarbon group which may be substituted by 1 to 4 substituent(s) selected from 1) a hydrocarbon group which may be substituted, 2) a heterocyclic group which may be substituted, 3) a C_{1-4} alkoxy group which may be substituted, 4) a C_{1-4} alkylthio group which may be substituted, 5) a C_{2-6} alkoxycarbonyl group which may be substituted, 6) a C_{1-6} alkanoyl group which may be substituted, 7) an amino group which may be substituted, 8) a cyclic amino group, 9) a halogen atom, 10) a nitro group, 11) a cyano group, 12) a carbamoyl group which may be substituted, 13) a sulfamoyl group which may be substituted and 14) an acyl group derived from a sulfonic acid.

5. The compound as claimed in claim 1, wherein R^1 is a hydrocarbon group which may be substituted by 1 to 4 substituent(s) selected from 1) a hydrocarbon group which may be substituted, 2) a heterocyclic group which may

be substituted, 3) a C₁₋₄ alkoxy group which may be substituted, 4) a C₁₋₄ alkylthio group which may be substituted, 5) a C₂₋₆ alkoxy carbonyl group which may be substituted, 6) an amino group which may be substituted, 7) a halogen atom, 8) a nitro group and 9) a cyano group.

- 5 6. The compound as claimed in claim 1, wherein R¹ is a hydrocarbon group which may be substituted by 1 to 4 substituent(s) selected from 1) a hydrocarbon group which may be substituted, 2) a heterocyclic group which may be substituted, 3) a C₁₋₄ alkylthio group which may be substituted, 4) a C₂₋₆ alkoxy carbonyl group which may be substituted, 5) an amino group which may be substituted, 6) a halogen atom and 7) a nitro group.
- 10 7. The compound as claimed in claim 1, wherein R² is an cyclic hydrocarbon group which may be substituted.
8. The compound as claimed in claim 1, wherein R³ is a halogen, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted or an acyl group derived from a sulfonic acid.
- 15 9. The compound as claimed in claim 1, wherein R³ is a halogen.
10. The compound as claimed in claim 1, wherein R⁴ is a hydrogen atom.
11. The compound as claimed in claim 1, wherein n is 0.
- 20 12. The compound as claimed in claim 1, wherein R¹ is a hydrocarbon group selected from Group 3 which may be substituted by member(s) selected from Group 1;

R² is a cyclic hydrocarbon group selected from Group 10 which may be substituted by member(s) selected from Group 2, or a heterocyclic group selected from Group 4 which may be substituted by member(s) selected from Group 2;

R³ is a halogen atom, a carbamoyl group, a N-mono-substituted carbamoyl group which is substituted by a member selected from Group 11, a N,N-di-substituted carbamoyl group which is substituted by a member selected from Group 11 and a member selected from Group 14, a cyclic aminocarbonyl group selected from Group 17, a sulfamoyl group, N-mono-substituted sulfamoyl group which is substituted by a member selected from Group 11, a N,N-di-substituted sulfamoyl group which is substituted by a member selected from Group 11 and a member selected from Group 14, a cyclic aminosulfonyl group selected from Group 20, an acyl group derived from a sulfonic acid selected from Group 15, a C₁₋₄ alkyl group which may be substituted by member (s) selected from Group 2, a C₁₋₄ alkoxy group which may be substituted by member(s) selected from Group 2, an amino group which may be substituted by member(s) selected from Group 8, a cyclic amino group selected from Group 9, a nitro group or a cyano group.

[In the above,

Group 1 includes

1) a hydrocarbon group selected from Group 3 which may be substituted by member(s) selected from Group 2, 2) a heterocyclic group selected from Group 4 which may be substituted by member(s) selected from Group 2, 3) a C₁₋₄ alkoxy group which may be substituted by member(s) selected from Group 2, 4) a C₁₋₄ alkylthio group which may be substituted by member(s) selected from Group 2, 5) a C₂₋₆ alkoxy carbonyl group which may be substituted by member(s) selected from Group 2, 6) a C₁₋₆ alkanoyl group, 7) an amino group which may be substituted by member(s) selected from Group 8, 8) a cyclic amino group selected from Group 9, 9) a halogen atom, 10) a nitro group, 11) a cyano group, 12) a carbamoyl group, 13) a mono-substituted carbamoyl group which is substituted by a member selected from Group 11, 14) di-substituted carbamoyl group which is substituted by a member selected from Group 11 and a member selected Group 14, 15) a cyclic amino carbamoyl group selected from Group 17, 16) a sulfamoyl group, 17) a N-mono substituted sulfamoyl group which is substituted by a member selected from Group 11, 18) a N,N-di-substituted sulfamoyl group which is substituted by a member selected from Group 11 and a member selected Group 14, and 19) an acyl group derived from a sulfonic acid selected from Group 19,

Group 2 includes

1) a C₁₋₆ alkoxy group, 2) a halogen atom, 3) a C₁₋₆ alkyl group, 4) a C₁₋₄ alkynyl group, 5) an amino group, 6) a hydroxy group, 7) a cyano group and 8) an amidino group,

Group 3 includes

1) a C₁₋₆ alkyl group, 2) a C₃₋₈ cycloalkyl group and 3) a C₆₋₁₄ aryl group,

Group 4 includes

1) an aromatic monocyclic heterocyclic group selected from Group 5, 2) an aromatic condensed heterocyclic group selected from Group 6 and 3) a saturated or unsaturated non-aromatic heterocyclic group selected from Group 7.

Group 5 includes

furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl,

Group 6 includes

benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzindazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, benzopyranyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalyl, phthalazinyl, naphthylidynyl, purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl,

Group 7 includes

oxylanyl, azetidynyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl,

Group 8 includes

1) a C_{1-6} alkyl, 2) a C_{1-6} alkanoyl, 3) a C_{7-13} arylcarbonyl, 4) an optionally halogenated C_{2-6} alkoxy carbonyl, 5) a C_{1-6} alkylimidoyl, 6) a formylimidoyl and 7) an amidino,

Group 9 includes

1) 1-azetidynyl, 2) 1-pyrrolidinyl, 3) 1-piperidinyl, 4) 4-morpholinyl, 5) 1-piperazinyl and 6) 1-piperazinyl which may have a C_{1-6} alkyl, a C_{7-10} aralkyl or a C_{6-10} aryl at 4-position,

Group 10 includes

C_{3-9} cycloalkyl, 1-indanyl, 2-indanyl, C_{3-6} cycloalkenyl, C_{4-6} cycloalkanedienyl and C_{6-14} aryl,

Group 11 includes

1) a C_{1-6} alkyl group which may be substituted by member(s) selected from Group 12, 2) a C_{3-6} cycloalkyl group which may be substituted by member(s) selected from Group 12, 3) a C_{6-10} aryl group which may be substituted by member(s) selected from Group 12, 4) a C_{7-10} aralkyl group which may be substituted by member(s) selected from Group 12, 5) a C_{1-6} alkoxy group which may be substituted by member(s) selected from Group 12 and 6) a heterocyclic group selected from Group 13 which may be substituted by member(s) selected from Group 12,

Group 12 includes

1) a hydroxy group, 2) an amino group, 3) an amino group which is mono or di-substituted by member(s) selected from Group 16, 4) a halogen atom, 5) a nitro group, 6) a cyano group, 7) a C_{1-6} alkyl group which may be substituted by halogen atom(s) and 8) a C_{1-6} alkoxy group which may be substituted by halogen atom(s),

Group 13 includes

1) an aromatic heterocyclic group selected from Group 5 and Group 6 and 2) a saturated or unsaturated non-aromatic heterocyclic group selected from Group 7, each of which contains at least one heteroatom(s) selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom,

Group 14 includes

a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group and a C_{7-10} aralkyl group,

Group 15 includes

1) a C_{1-10} alkylsulfonyl which may be substituted by member(s) selected from Group 12, 2) a C_{2-6} alkenylsulfonyl which may be substituted by member(s) selected from Group 12, 3) a C_{2-6} alkynylsulfonyl which may be substituted by member(s) selected from Group 12, 4) a C_{3-9} cycloalkylsulfonyl which may be substituted by member(s) selected from Group 12, 5) a C_{3-9} cycloalkenylsulfonyl which may be substituted by member(s) selected from Group 12, 6) a C_{6-14} arylsulfonyl which may be substituted by member(s) selected from Group 12 and 7) a C_{7-10} aralkylsulfonyl which may be substituted by member(s) selected from Group 12,

Group 16 includes

a C_{1-6} alkyl group, a C_{1-6} alkanoyl, a C_{7-13} arylcarbonyl and a C_{1-6} alkylsulfonyl,

Group 17 includes

1-azetidinylicarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, 4-morpholinylcarbonyl and 1-piperazinylcarbonyl which may be substituted by member(s) selected from Group 18,

Group 18 includes

a C₁₋₆ alkyl group, a C₇₋₁₀ aralkyl group and a C₆₋₁₀ aryl group,
Group 19 includes

a C₁₋₁₀ alkylsulfonyl which may be substituted by member(s) selected from Group 12, a C₂₋₆ alkenylsulfonyl which may be substituted by member(s) selected from Group 12, a C₂₋₆ alkynylsulfonyl which may be substituted by member(s) selected from Group 12, a C₃₋₉ cycloalkylsulfonyl which may be substituted by member(s) selected from Group 12, a C₃₋₉ cycloalkenylsulfonyl which may be substituted by member(s) selected from Group 12, a C₆₋₁₄ arylsulfonyl which may be substituted by member(s) selected from Group 12, and a C₇₋₁₀ aralkylsulfonyl which may be substituted by member(s) selected from Group 12, and

Group 20 includes

1-azetidinylsulfonyl, 1-pyrrolidinylsulfonyl, 1-piperidinylsulfonyl, 4-morpholinylsulfonyl and 1-piperazinylsulfonyl which may be substituted by member(s) selected from Group 18].

13. The compound as claimed in claim 1, wherein R¹ is a C₃₋₈ cycloalkyl group which may be substituted by member(s) selected from Group 1 or a C₆₋₁₄ aryl group which may be substituted by member(s) selected from Group 1.

14. The compound as claimed in claim 12, wherein R¹ is 1) a C₆₋₁₄ aryl group which may be substituted by a halogen atom, a C₁₋₆ alkyl which may be substituted by halogen(s), a C₁₋₄ alkylthio, a nitro, a carbamoyl, a sulfamoyl or C₁₋₆ alkylsulfonyl, 2) a C₁₋₆ alkyl group which may be substituted by (i) a C₂₋₆ alkoxycarbonyl group or (ii) a C₁₋₆ alkyl group which may be substituted by phenyl(s) which may be substituted by C₁₋₆ alkyl(s) or 3) a C₃₋₈ cycloalkyl group which may be substituted by (i) a halogen atom, (ii) a C₁₋₆ alkyl(s) which may be substituted by halogen(s) or (iii) a C₁₋₆ alkoxy group which may be substituted by halogen(s);

R² is a phenyl group which may be substituted by a halogen atom, a C₁₋₆ alkyl, a C₁₋₄ alkoxy or a cyano, a C₃₋₈ cycloalkyl group or a pyridyl group;

R³ is (i) a halogen atom, (ii) a carbamoyl group, (iii) a sulfamoyl group which may have one or two of C₁₋₆ alkyl(s) and

C₃₋₆ cycloalkyl(s) at N-atoms, a cyclic aminosulfonyl group which is selected from Group 20, a C₁₋₆ alkylsulfonyl group, or

C₃₋₆ cycloalkylsulfonyl group;

R⁴ is a hydrogen atom;

n is 0 or 1, and

p is 0 or 1.

15. The compound as claimed in claim 12, wherein

R¹ is 1) a phenyl group which may be substituted by a halogen atom, a C₁₋₃ alkyl, trifluoromethyl, methoxy, trifluoromethoxy, methylthio or nitro, 2) a naphthyl, 3) a C₁₋₆ alkyl group which may be substituted by (i) a C₂₋₃ alkoxycarbonyl which may be substituted, (ii) phenyl or (iii) 3-isopropenylphenyl or 4) cyclohexyl;

R² is a phenyl group which may be substituted by a halogen atom, methyl, methoxy or cyano, a cyclohexyl group or a 3-pyridyl group;

R³ is (i) a halogen atom, (ii) a carbamoyl group, (iii) a 4-morpholinylsulfonyl group or (iv) a methylsulfonyl group;

R⁴ is a hydrogen atom;

n is 0 or 1; and

p is 0 or 1.

16. The compound as claimed in claim 12, wherein

R¹ is a phenyl group which may be substituted by a halogen atom or a C₁₋₃ alkyl;

R² is a phenyl group which may be substituted by halogen atom or methyl(s);

R³ is (i) a halogen atom, (ii) a carbamoyl group, (iii) a sulfamoyl group which may be substituted by one or two members selected C₁₋₆ alkyl and C₃₋₆ cycloalkyl at N-atoms, a cyclic aminosulfonyl group selected from Group 20, a C₁₋₆ alkylsulfonyl group or a C₃₋₆ cycloalkyl sulfonyl group;

R⁴ is a hydrogen atom;

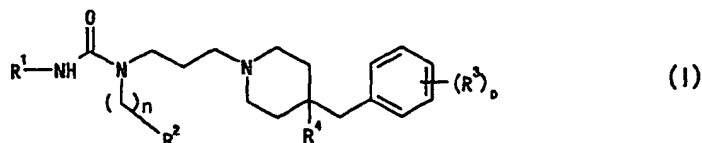
n is 0; and

p is 0 or 1.

17. The compound as claimed in claim 1, which is N-[3-(4-benzyl-1-piperidinyl)propyl]-N'-(4-chlorophenyl)-N-phenylurea, N'-(4-chlorophenyl)-N-[3-[4-(4-fluorobenzyl)-1-piperidinyl]propyl]-N-phenylurea, N'-(4-chlorophenyl)-N-(3-

{4-[4-(4-morpholinylsulfonyl)benzyl]-1-piperidiny]propyl}-N-phenylurea, N'-(4-chlorophenyl)-N-(3-{4-[4-(4-methylsulfonyl)benzyl]-1-piperidiny]propyl}-N-phenylurea or 4-[[1-(3-[[[4-chloroanilino)carbonyl]anilino)propyl]-4-piperidiny]methyl]benzamide, or a salt thereof.

18. A prodrug of a compound of the formula:

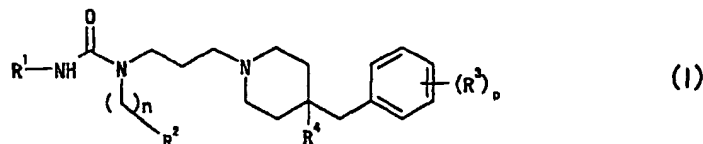


[wherein

R¹ is a hydrocarbon group which may be substituted;
 R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;
 R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;
 R⁴ is a hydrogen atom or a hydroxy group;
 n is an integer of 0 or 1;
 p is an integer of 0 or 1 to 4];

or salt thereof.

19. A pharmaceutical composition containing a compound of the formula:



[wherein

R¹ is a hydrocarbon group which may be substituted;
 R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;
 R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;
 R⁴ is a hydrogen atom or a hydroxy group;
 n is an integer of 0 or 1;
 p is an integer of 0 or 1 to 4];

or a salt thereof or a prodrug thereof.

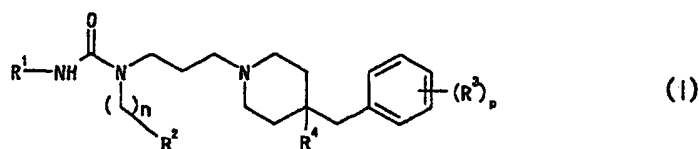
20. The pharmaceutical composition as claimed in claim 19, which is a chemokine receptor antagonist.

21. The pharmaceutical composition as claimed in claim 19, which is a CCR5 antagonist.

22. The composition as claimed in claim 19, which is for the treatment or prevention of infectious disease of HIV.

23. The composition as claimed in claim 19, which is for the treatment or prevention of AIDS.

24. The composition as claimed in claim 19, which is for the prevention of the progression of AIDS.
25. The composition as claimed in claim 22, further comprises a protease inhibitor and/or a reverse transcriptase inhibitor.
26. The composition as claimed in claim 25, wherein the reverse transcriptase inhibitor is zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, nevirapine, delavirdine or efavirenz.
27. The composition as claimed in claim 25, wherein the protease inhibitor is saquinavir, ritonavir, indinavir, amprenavir or nelfinavir.
28. Use of a compound of the formula:

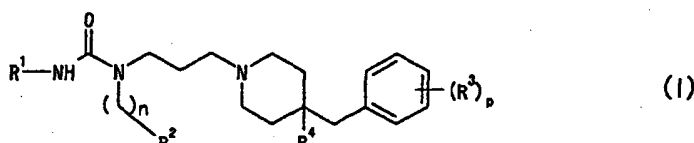


[wherein

- R¹ is a hydrocarbon group which may be substituted;
 R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;
 R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;
 R⁴ is a hydrogen atom or a hydroxy group;
 n is an integer of 0 or 1;
 p is an integer of 0 or 1 to 4];

or a salt thereof or a prodrug thereof for manufacturing an antagonist of a chemokine receptor.

29. Use of a compound of the formula:

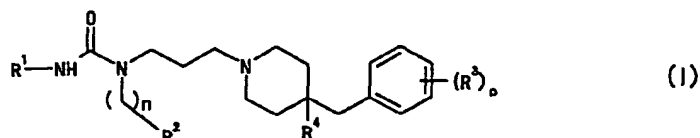


[wherein

- R¹ is a hydrocarbon group which may be substituted;
 R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;
 R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;
 R⁴ is a hydrogen atom or a hydroxy group;
 n is an integer of 0 or 1;
 p is an integer of 0 or 1 to 4];

a salt thereof or a prodrug thereof for manufacturing a CCR5 antagonist.

30. Use of a compound of the formula:



10 [wherein

R¹ is a hydrocarbon group which may be substituted;

R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;

R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;

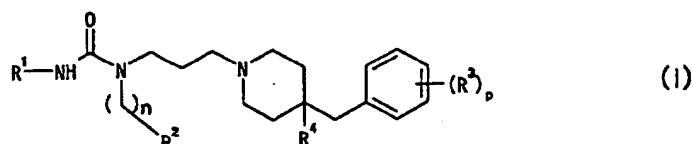
R⁴ is a hydrogen atom or a hydroxy group;

n is an integer of 0 or 1;

p is an integer of 0 or 1 to 4];

20 a salt thereof or a prodrug thereof for manufacturing a medicament for the treatment or prevention of infectious disease of HIV.

31. Use of a compound of the formula:



[wherein

R¹ is a hydrocarbon group which may be substituted;

R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;

R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;

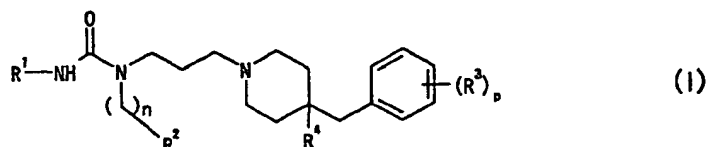
R⁴ is a hydrogen atom or a hydroxy group;

n is an integer of 0 or 1;

p is an integer of 0 or 1 to 4];

45 a salt thereof or a prodrug thereof, for the manufacture of a medicament for the treatment or prevention of infectious disease of HIV which is used in combination with a protease inhibitor and/or a reverse transcriptase inhibitor.

32. A method for antagonizing CCR5 which comprises administering to a mammal in need thereof an effective amount of the compound of the formula (I):

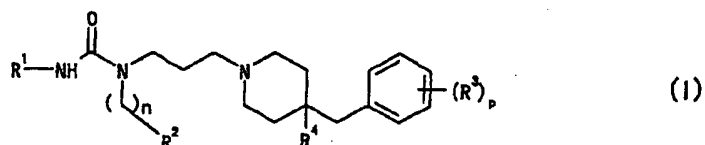


[wherein

R¹ is a hydrocarbon group which may be substituted;
 R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;
 R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;
 R⁴ is a hydrogen atom or a hydroxy group;
 n is an integer of 0 or 1;
 p is an integer of 0 or 1 to 4];

a salt thereof or a prodrug thereof.

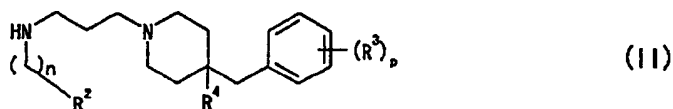
33. A method for producing a compound of the formula:



[wherein

R¹ is a hydrocarbon group which may be substituted;
 R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;
 R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;
 R⁴ is a hydrogen atom or a hydroxy group;
 n is an integer of 0 or 1;
 p is an integer of 0 or 1 to 4];

or a salt thereof, which comprises reacting a compound of the formula:

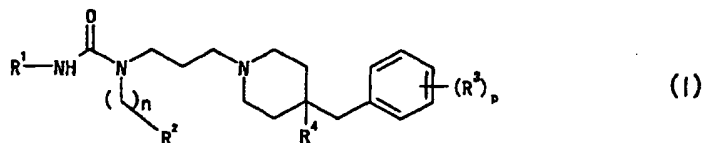


[wherein each symbol has the same meaning as above], or a salt thereof, with a compound of the formula:



[wherein R¹ has the meaning given above], or a salt thereof.

34. A method for producing a compound of the formula:



[wherein

R¹ is a hydrocarbon group which may be substituted;

R² is a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted;

R³ is a halogen atom, a carbamoyl group which may be substituted, a sulfamoyl group which may be substituted, an acyl group derived from a sulfonic acid, a C₁₋₄ alkyl group which may be substituted, a C₁₋₄ alkoxy group which may be substituted, an amino group which may be substituted, a nitro group or a cyano group;

R⁴ is a hydrogen atom or a hydroxy group;

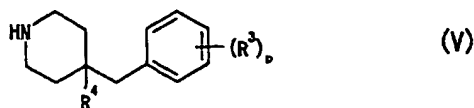
n is an integer of 0 or 1;

p is an integer of 0 or 1 to 4];

or a salt thereof, which comprises reacting a compound of the formula:



[wherein X is a leaving group, and the other symbols have the meanings given above], or a salt thereof, with a compound of the formula:



[wherein each symbol has the meaning given above], or a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/06908

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.⁷ C07D211/14, C07D211/18, A61K31/445, A61P43/00, A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.⁷ C07D211/14, C07D211/18, A61K31/445, A61P43/00, A61P31/18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN), CAPLUS (STN), CAOLD (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PA	WO, 00/35454, A1 (DU PONT PHARMACEUTICALS COMPANY), 22 June, 2000 (22.06.00) (Family: none)	1-31, 33, 34
A	EP, 747357, A2 (BRISTOL-MYERS SQUIBB COMPANY), 11 December, 1996 (11.12.96) & JP, 9-3045, A & CA, 2177110, AA & AU, 9654758, A1 & US, 5668151, A	1-31, 33, 34
A	JP, 9-255572, A (Takeda Chemical Industries, Ltd.), 30 September, 1997 (30.09.97) (Family: none)	19-31

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
 - "E" earlier document but published on or after the international filing date
 - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - "O" document referring to an oral disclosure, use, exhibition or other means
 - "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search
07 December, 2000 (07.12.00)Date of mailing of the international search report
19 December, 2000 (19.12.00)Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/06908

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 32
because they relate to subject matter not required to be searched by this Authority, namely:
Since humans fall within the scope of mammals, the invention as set forth in claim 32 corresponds to invention pertaining to methods for treatment of the human body by therapy.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

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